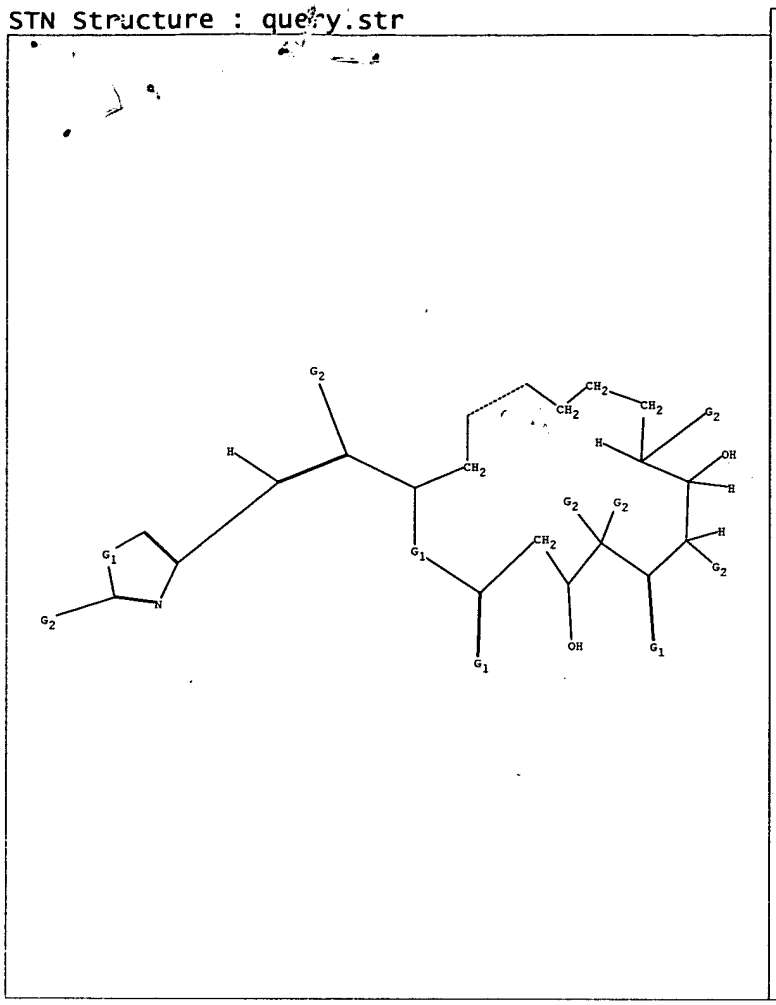
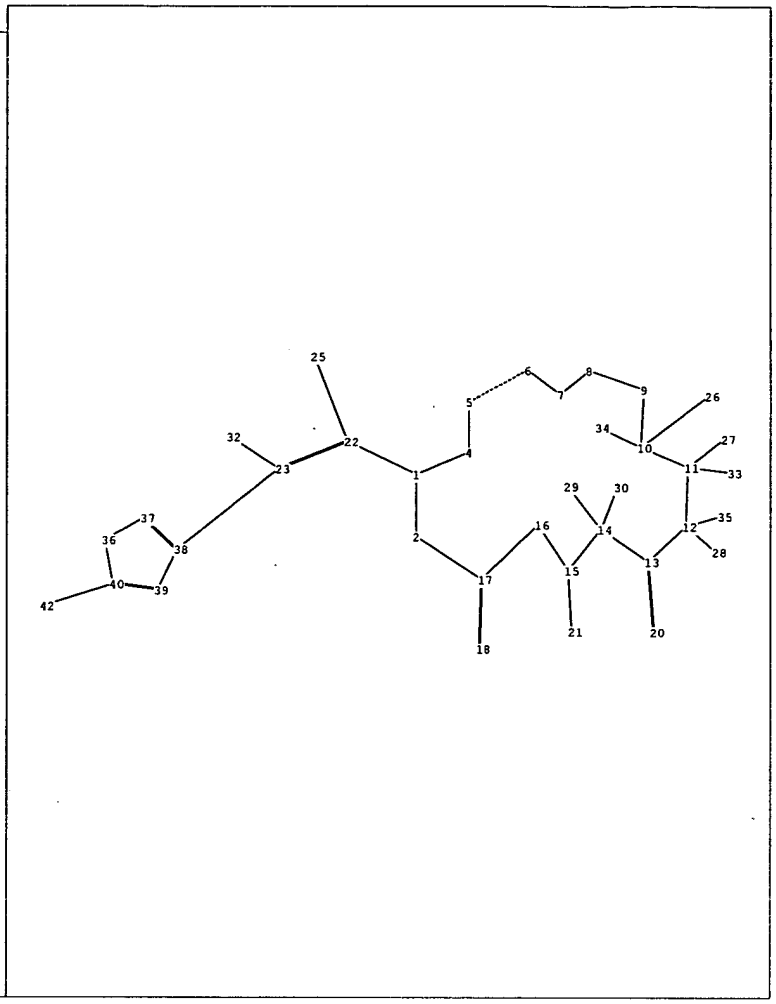
STN Structure : query.str





chain nodes :
18 20 21 22 23 25 26 27 28 29 30 32 33 34 35 42
ring nodes :
1 2 4 5 6 7 8 9 10 11 12 13 14 15 16 17 36 37 38 39 40
chain bonds :
1-22 10-26 10-34 11-27 11-33 12-28 12-35 13-20 14-30 14-29 15-21 17-18 22-23
22-25 23-32 23-38 40-42
ring bonds :
1-2 1-4 2-17 4-5 5-6 6-7 7-8 8-9 9-10 10-11 11-12 12-13 13-14 14-15 15-16
16-17 36-37 36-40 37-38 38-39 39-40
exact/norm bonds :
1-2 1-4 1-22 2-17 4-5 5-6 6-7 7-8 8-9 9-10 10-11 10-26 10-34 11-12 11-27
11-33 12-13 12-28 12-35 13-14 13-20 14-15 14-30 14-29 15-16 15-21 16-17 17-18
22-23 22-25 23-32 23-38 36-37 36-40 37-38 38-39 39-40 40-42
isolated ring systems :
containing 1 : 36 :

G1:O,S

G2:CH3,Et

Match level :
1:Atom 2:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom 11:Atom 12:Atom
13:Atom 14:Atom 15:Atom 16:Atom 17:Atom 18:Atom 20:Atom 21:CLASS 22:CLASS
23:CLASS 25:CLASS 26:CLASS 27:CLASS 28:CLASS 29:CLASS 30:CLASS 32:CLASS 33:CLASS
34:CLASS 35:CLASS 36:Atom 37:Atom 38:Atom 39:Atom 40:Atom 42:CLASS

```
* * * * * * * * * *  Welcome to STN International  * * * * * * * * * *

NEWS  1          Web Page URLs for STN Seminar Schedule - N. America
NEWS  2  Apr 08  "Ask CAS" for self-help around the clock
NEWS  3  Apr 09  BEILSTEIN: Reload and Implementation of a New Subject Area
NEWS  4  Apr 09  ZDB will be removed from STN
NEWS  5  Apr 19  US Patent Applications available in IFICDB, IFIPAT, and IFIUDB
NEWS  6  Apr 22  Records from IP.com available in CAPLUS, HCAPLUS, and ZCAPLUS
NEWS  7  Apr 22  BIOSIS Gene Names now available in TOXCENTER
NEWS  8  Apr 22  Federal Research in Progress (FEDRIP) now available
NEWS  9  Jun 03  New e-mail delivery for search results now available
NEWS 10  Jun 10  MEDLINE Reload
NEWS 11  Jun 10  PCTFULL has been reloaded
NEWS 12  Jul 02  FOREGE no longer contains STANDARDS file segment
NEWS 13  Jul 22  USAN to be reloaded July 28, 2002;
                 saved answer sets no longer valid
NEWS 14  Jul 29  Enhanced polymer searching in REGISTRY
NEWS 15  Jul 30  NETFIRST to be removed from STN
NEWS 16  Aug 08  CANCERLIT reload
NEWS 17  Aug 08  PHARMAMarketLetter(PHARMAML) - new on STN
NEWS 18  Aug 08  NTIS has been reloaded and enhanced
NEWS 19  Aug 09  JAPIO to be reloaded August 25, 2002
NEWS 20  Aug 19  Aquatic Toxicity Information Retrieval (AQUIRE)
                 now available on STN
NEWS 21  Aug 19  IFIPAT, IFICDB, and IFIUDB have been reloaded
NEWS 22  Aug 19  The MEDLINE file segment of TOXCENTER has been reloaded

NEWS EXPRESS  February 1 CURRENT WINDOWS VERSION IS V6.0d,
              CURRENT MACINTOSH VERSION IS V6.0a(ENG) AND V6.0Ja(JP),
              AND CURRENT DISCOVER FILE IS DATED 05 FEBRUARY 2002
NEWS HOURS    STN Operating Hours Plus Help Desk Availability
NEWS INTER    General Internet Information
NEWS LOGIN    Welcome Banner and News Items
NEWS PHONE    Direct Dial and Telecommunication Network Access to STN
NEWS WWW      CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that
specific topic.

  All use of STN is subject to the provisions of the STN Customer
  agreement.  Please note that this agreement limits use to scientific
  research.  Use for software development or design or implementation
  of commercial gateways or other similar uses is prohibited and may
  result in loss of user privileges and other penalties.

  * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * *


FILE 'HOME' ENTERED AT 16:57:10 ON 22 AUG 2002

=> file reg
COST IN U.S. DOLLARS                            SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                                 0.21       0.21

FILE 'REGISTRY' ENTERED AT 16:57:18 ON 22 AUG 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2002 American Chemical Society (ACS)

STRUCTURE FILE UPDATES:   21 AUG 2002  HIGHEST RN 444646-89-3
DICTIONARY FILE UPDATES:  21 AUG 2002  HIGHEST RN 444646-89-3
```

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

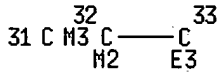
Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

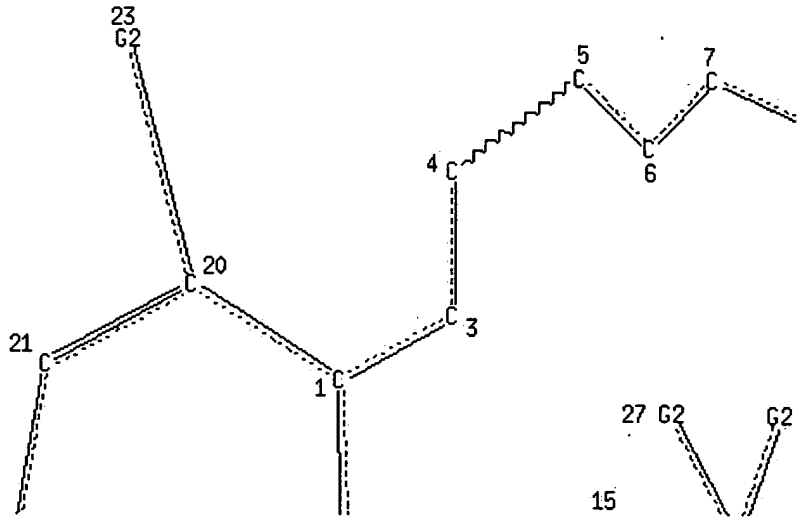
Calculated physical property data is now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=>
L1 STRUCTURE UPLOADED

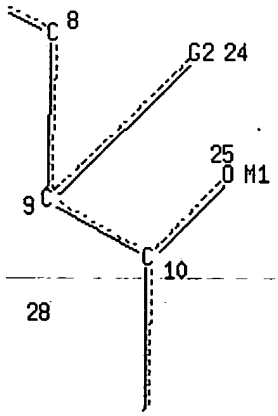
=> d l1
L1 HAS NO ANSWERS
L1 STR



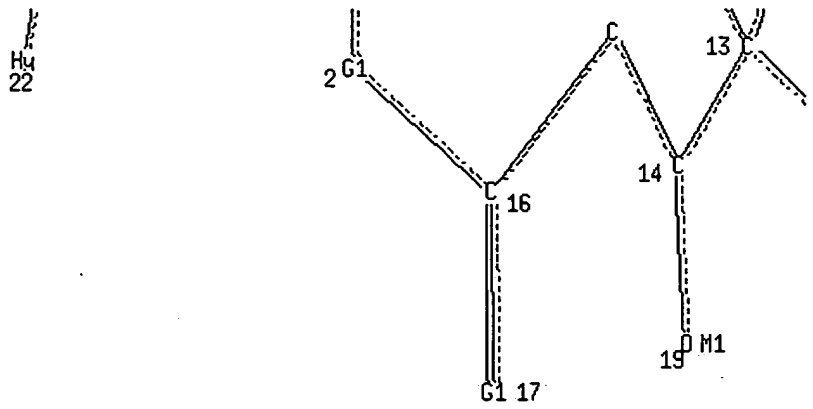
0 29 S 30



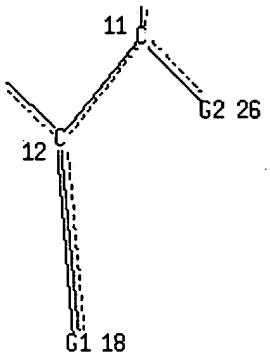
Page 1-A



Page 1-B



Page 2-A



Page 2-B
VAR G1=29/30
VAR G2=31/32
NODE ATTRIBUTES:

HCOUNT	IS M1	AT	19
HCOUNT	IS M1	AT	25
HCOUNT	IS M3	AT	31
HCOUNT	IS M2	AT	32
HCOUNT	IS E3	AT	33
NSPEC	IS R	AT	1
NSPEC	IS R	AT	2
NSPEC	IS R	AT	3
NSPEC	IS R	AT	4
NSPEC	IS R	AT	5
NSPEC	IS R	AT	6
NSPEC	IS R	AT	7
NSPEC	IS R	AT	8
NSPEC	IS R	AT	9
NSPEC	IS R	AT	10
NSPEC	IS R	AT	11
NSPEC	IS R	AT	12
NSPEC	IS R	AT	13
NSPEC	IS R	AT	14
NSPEC	IS R	AT	15
NSPEC	IS R	AT	16
NSPEC	IS C	AT	17
NSPEC	IS C	AT	18
NSPEC	IS C	AT	19
NSPEC	IS C	AT	20
NSPEC	IS C	AT	21
NSPEC	IS C	AT	22
NSPEC	IS C	AT	23
NSPEC	IS C	AT	24
NSPEC	IS C	AT	25

```
NSPEC   IS C      AT  26
NSPEC   IS C      AT  27
NSPEC   IS C      AT  28
DEFAULT MLEVEL IS ATOM
MLEVEL  IS CLASS  AT  19 20 21 25 31 32 33
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC I
NUMBER OF NODES IS  33

STEREO ATTRIBUTES: NONE


=> s l1
SAMPLE SEARCH INITIATED 17:02:40 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -   1318 TO ITERATE

 75.9% PROCESSED    1000 ITERATIONS                          11 ANSWERS
INCOMPLETE SEARCH (SYSTEM LIMIT EXCEEDED)
SEARCH TIME: 00.00.02

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:        24183 TO    28537
PROJECTED ANSWERS:              61 TO      517

L2           11 SEA SSS SAM L1

=> s l1 full
THE ESTIMATED SEARCH COST FOR FILE 'REGISTRY' IS 139.90 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N or END:y
FULL SEARCH INITIATED 17:02:49 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -  25969 TO ITERATE

100.0% PROCESSED   25969 ITERATIONS                         235 ANSWERS
SEARCH TIME: 00.00.06

L3          235 SEA SSS FUL L1

=> file hcaplus
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                 ENTRY    SESSION
FULL ESTIMATED COST                             143.32     143.53

FILE 'HCAPLUS' ENTERED AT 17:02:57 ON 22 AUG 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2002 AMERICAN CHEMICAL SOCIETY (ACS)


Copyright of the articles to which records in this database refer is
held by the publishers listed in the PUBLISHER (PB) field (available
for records published or updated in Chemical Abstracts after December
26, 1996), unless otherwise indicated in the original publications.
The CA Lexicon is the copyrighted intellectual property of the
the American Chemical Society and is provided to assist you in searching
databases on STN.  Any dissemination, distribution, copying, or storing
of this information, without the prior written consent of CAS, is
strictly prohibited.

FILE COVERS 1907 - 22 Aug 2002  VOL 137 ISS 8
FILE LAST UPDATED: 21 Aug 2002  (20020821/ED)

 This file contains CAS Registry Numbers for easy and accurate
```

substance identification.

CAS roles have been modified effective December 16, 2001. Please check your SDI profiles to see if they need to be revised. For information on CAS roles, enter HELP ROLES at an arrow prompt or use the CAS Roles thesaurus (/RL field) in this file.

=> **s l3**
L4 134 L3

=> **file reg**

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	2.14	145.67

FILE 'REGISTRY' ENTERED AT 17:03:04 ON 22 AUG 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

STRUCTURE FILE UPDATES: 21 AUG 2002 HIGHEST RN 444646-89-3
DICTIONARY FILE UPDATES: 21 AUG 2002 HIGHEST RN 444646-89-3

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

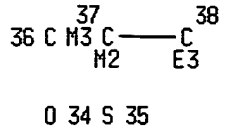
Please note that search-term pricing does apply when conducting SmartSELECT searches.

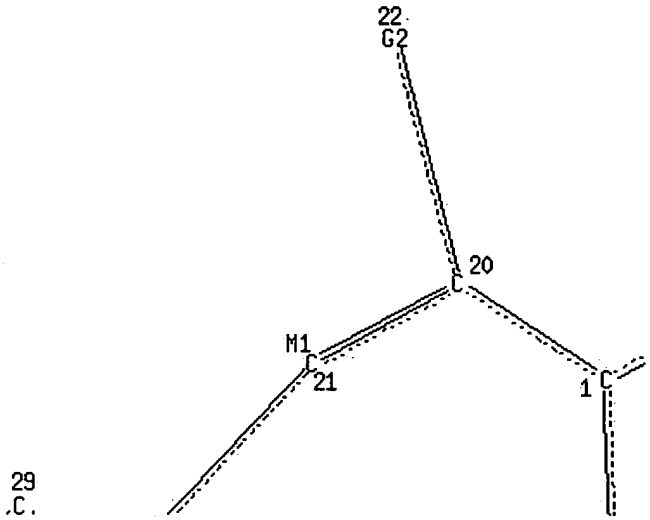
Crossover limits have been increased. See HELP CROSSOVER for details.

Calculated physical property data is now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

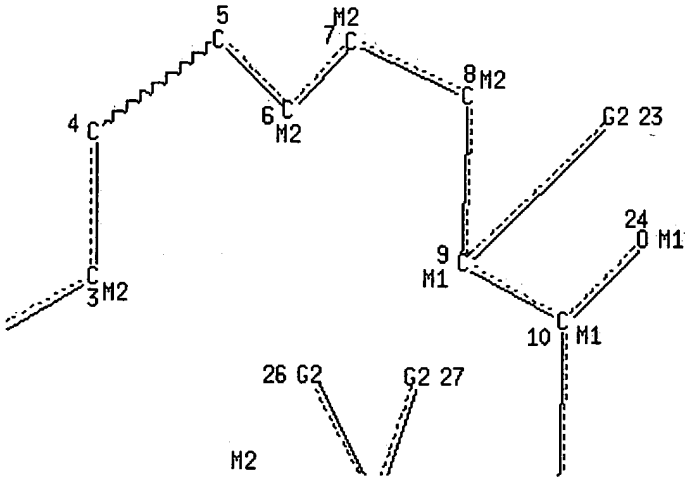
=>
L5 STRUCTURE UPLOADED

=> **d l5**
L5 HAS NO ANSWERS
L5 STR

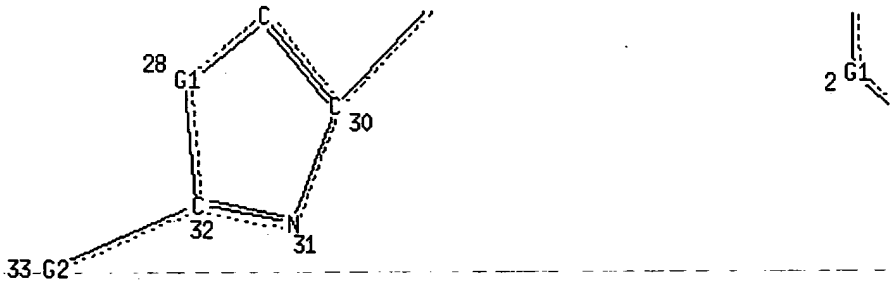




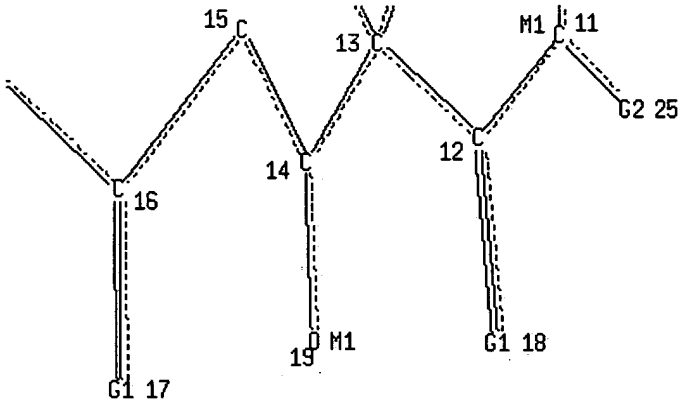
Page 1-A



Page 1-B



Page 2-A



Page 2-B
VAR G1=34/35
VAR G2=36/37
NODE ATTRIBUTES:

HCOUNT	IS M2	AT	3
HCOUNT	IS M2	AT	6
HCOUNT	IS M2	AT	7
HCOUNT	IS M2	AT	8
HCOUNT	IS M1	AT	9
HCOUNT	IS M1	AT	10
HCOUNT	IS M1	AT	11
HCOUNT	IS M2	AT	15
HCOUNT	IS M1	AT	19
HCOUNT	IS M1	AT	21
HCOUNT	IS M1	AT	24
HCOUNT	IS M3	AT	36
HCOUNT	IS M2	AT	37
HCOUNT	IS E3	AT	38
NSPEC	IS R	AT	1
NSPEC	IS R	AT	2
NSPEC	IS R	AT	3
NSPEC	IS R	AT	4
NSPEC	IS R	AT	5
NSPEC	IS R	AT	6
NSPEC	IS R	AT	7
NSPEC	IS R	AT	8
NSPEC	IS R	AT	9
NSPEC	IS R	AT	10
NSPEC	IS R	AT	11
NSPEC	IS R	AT	12
NSPEC	IS R	AT	13
NSPEC	IS R	AT	14
NSPEC	IS R	AT	15
NSPEC	IS R	AT	16
NSPEC	IS C	AT	17
NSPEC	IS C	AT	18
NSPEC	IS C	AT	19
NSPEC	IS C	AT	20
NSPEC	IS C	AT	21
NSPEC	IS C	AT	22
NSPEC	IS C	AT	23
NSPEC	IS C	AT	24
NSPEC	IS C	AT	25
NSPEC	IS C	AT	26
NSPEC	IS C	AT	27
NSPEC	IS R	AT	28
NSPEC	IS R	AT	29
NSPEC	IS R	AT	30
NSPEC	IS R	AT	31

```
NSPEC   IS R      AT  32
NSPEC   IS C      AT  33
DEFAULT MLEVEL IS ATOM
MLEVEL  IS CLASS  AT  19 20 21 24 36 37 38
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC I
NUMBER OF NODES IS  38

STEREO ATTRIBUTES: NONE


=> s l5
SAMPLE SEARCH INITIATED 17:07:01 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -     59 TO ITERATE

100.0% PROCESSED      59 ITERATIONS                              8 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:          720 TO     1640
PROJECTED ANSWERS:               8 TO      329

L6            8 SEA SSS SAM L5

=> s l5 full
THE ESTIMATED SEARCH COST FOR FILE 'REGISTRY' IS 139.90 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N or END:y
FULL SEARCH INITIATED 17:07:08 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -   1042 TO ITERATE

100.0% PROCESSED    1042 ITERATIONS                          121 ANSWERS
SEARCH TIME: 00.00.03

L7          121 SEA SSS FUL L5

=> file hcaplus
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                 ENTRY    SESSION
FULL ESTIMATED COST                             142.56     288.23

FILE 'HCAPLUS' ENTERED AT 17:07:15 ON 22 AUG 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2002 AMERICAN CHEMICAL SOCIETY (ACS)


Copyright of the articles to which records in this database refer is
held by the publishers listed in the PUBLISHER (PB) field (available
for records published or updated in Chemical Abstracts after December
26, 1996), unless otherwise indicated in the original publications.
The CA Lexicon is the copyrighted intellectual property of the
the American Chemical Society and is provided to assist you in searching
databases on STN.  Any dissemination, distribution, copying, or storing
of this information, without the prior written consent of CAS, is
strictly prohibited.

FILE COVERS 1907 - 22 Aug 2002  VOL 137 ISS 8
FILE LAST UPDATED: 21 Aug 2002  (20020821/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.
```

CAS roles have been modified effective December 16, 2001. Please check your SDI profiles to see if they need to be revised. For information on CAS roles, enter HELP ROLES at an arrow prompt or use the CAS Roles thesaurus (/RL field) in this file.

=> **s l7**
L8 132 L7

=> s l8 and pd < september 1998
18872712 PD < SEPTEMBER 1998
(PD<19980900)
L9 34 L8 AND PD < SEPTEMBER 1998

=> **s l8 and klar, u?/au**
64 KLAR, U?/AU
L10 6 L8 AND KLAR, U?/AU

=> **s l9 and klar, u?/au**
64 KLAR, U?/AU
L11 0 L9 AND KLAR, U?/AU

=> **d l10, ibib abs fhitstr, 1-6**

L10 ANSWER 1 OF 6 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

ACCESSION NUMBER: 2002:132142 HCAPLUS
DOCUMENT NUMBER: 136:309773
TITLE: Synthesis and biological activity of epothilones
AUTHOR(S): **Klar, Ulrich**; Skuballa, Werner; Buchmann, Bernd; Schwede, Wolfgang; Bunte, Thomas; Hoffmann, Jens; Lichtner, Rosemarie B.
CORPORATE SOURCE: Research Laboratories of Schering AG, Berlin, D-13342, Germany
SOURCE: ACS Symposium Series (2001), 796(Anticancer Agents), 131-147
CODEN: ACSMC8; ISSN: 0097-6156
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

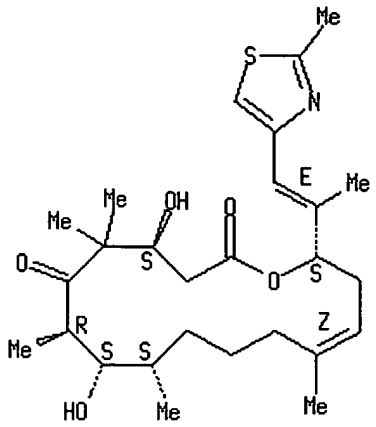
AB A review. The total synthesis and biol. activity of epothilone analogs are described. Selected SAR data indicate the possibility to improve activity and selectivity by structural modifications. The new compds. may help to elucidate the therapeutic potential of this class of anticancer drugs.

IT **189453-10-9D**, Epothilone D, analogs
RL: MSC (Miscellaneous)
(review of the synthesis and biol. activity of epothilones)

RN 189453-10-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 2 OF 6 HCAPLUS COPYRIGHT 2002 ACS

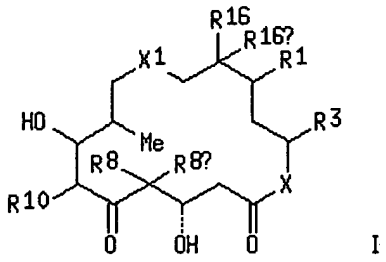
Full Text | Citing References

ACCESSION NUMBER: 2001:780370 HCAPLUS
DOCUMENT NUMBER: 135:331294
TITLE: Preparation of epothilone derivatives for pharmaceutical use in the treatment of cancer
INVENTOR(S): Buchmann, Bernd; **Klar, Ulrich**; Skuballa, Werner; Schwede, Wolfgang; Hoffmann, Jens; Lichtner, Rosemarie
PATENT ASSIGNEE(S): Schering A.-G., Germany
SOURCE: Ger. Offen., 42 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

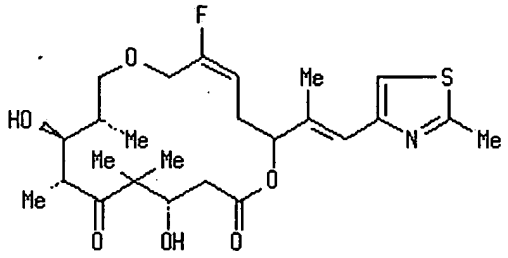
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10020517	A1	20011025	DE 2000-10020517	20000419
WO 2001081342	A2	20011101	WO 2001-EP4552	20010419
WO 2001081342	A3	20020510		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: DE 2000-10020517 A 20000419
OTHER SOURCE(S): MARPAT 135:331294
GI



I



II

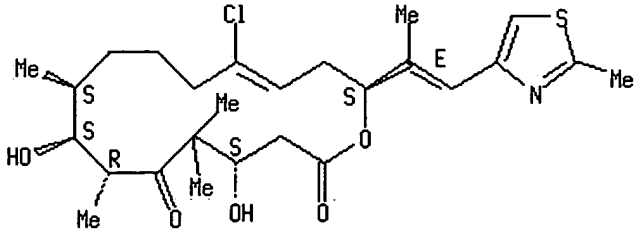
AB Epothilones, such as I [R3 = heteroaryl, heteroarylalkenyl, heteroarylhaloalkenyl,etc.; R8, R8a = H, alkyl, arylalkyl; R8R8a = alkylene, heteroalkene; R10 = H, alkyl, alkenyl, alkynyl; R1R16a = bond, O; R16 = H, CN, alkyl, halogen; X = O, NH; X1 = O, CH2], were prepd. for a variety of therapeutic uses, such as treatment of malignant tumors, proliferative diseases, leukemia, and chronic inflammatory diseases. Thus, epothilone II was prepd. via a multistep synthetic sequence starting from (3S)-dihydro-3-hydroxy-4,4-dimethyl-2(3H)-furanone, L-(-)-malic acid, and [(2-methyl-4-thiazolyl)methyl]phosphonic acid di-Et ester. Pharmaceutical formulations of the prepd. oxa-epothilones were discussed, but specific biol. activity data was not presented.

IT **369646-16-2P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of epothilone derivs. for pharmaceutical use in the treatment of cancer)

RN 369646-16-2 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 13-chloro-4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,16S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as described by E or Z.



L10 ANSWER 3 OF 6 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

ACCESSION NUMBER: 2001:729040 HCAPLUS
DOCUMENT NUMBER: 136:95676
TITLE: Subcellular distribution of epothilones in human tumor cells
AUTHOR(S): Lichtner, R. B.; Rotgeri, A.; Bunte, T.; Buchmann, B.; Hoffmann, J.; Schwede, W.; Skuballa, W.; **Klar, U.**

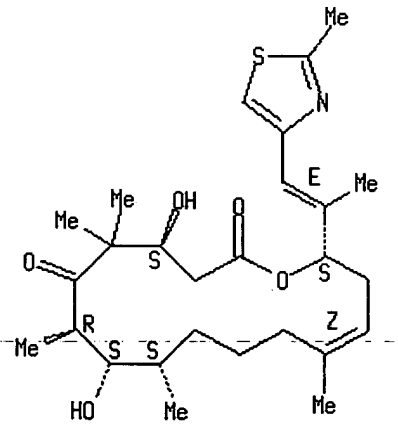
CORPORATE SOURCE: Research Laboratories of Schering AG, Berlin, 13342, Germany
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2001), 98(20), 11743-11748
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Epothilones are a new class of natural and potent antineoplastic agents that stabilize microtubules. Although 12,13-epoxide derivs. are potent antiproliferative agents, the activities of the corresponding 12,13-olefin analogs are significantly decreased. These data were confirmed for two new analogs, 6-propyl-EpoB (pEB) and 6-propyl-EpoD (pED), in comparison with the natural compds. EpoB/EpoD, by using human A431, MCF7, and MDR1-overexpressing NCl/Adr cells. By using tritiated pEB/pED, compd. uptake, release, and nuclear accumulation were investigated in A431 and NCl/Adr cells. In these cells, epothilones can principally be recognized and exported by verapamil-sensitive efflux pumps, which are not identical to MDR1. The degree of export depends on the structure, olefin vs. epoxide-analog, and also on the intracellular drug concn. The accumulation of pED used at 3.5 or 70 nM, resp., was increased in the presence of 10 μM Verapamil in both cell lines 2- to 8-fold. In contrast, the intracellular levels of pEB were affected by Verapamil only at 3.5 nM pEB in NCl/Adr (2-fold) and not in A431 cells. In addn., strong nuclear accumulation was obsd. for pEB (40-50%) but not paclitaxel or pED (5-15%) in both cell lines. Our study suggests that differences in growth inhibitory efficacy between epoxide and olefin analogs may be based on different mechanisms of drug accumulation and subcellular distribution.

IT **189453-10-9**, Epothilone D
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(subcellular distribution of antitumor epothilones in human tumor cells)

RN 189453-10-9 HCAPLUS
CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

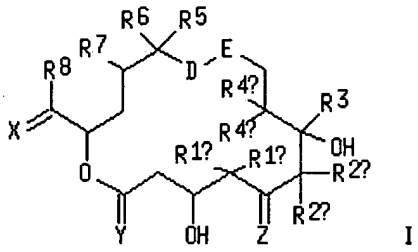
L10 ANSWER 4 OF 6 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

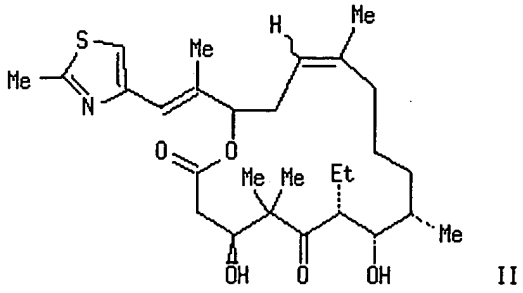
ACCESSION NUMBER: 2000:738730 HCAPLUS
DOCUMENT NUMBER: 133:309795
TITLE: Preparation of new epothilone derivatives and their pharmaceutical uses
INVENTOR(S): **Klar, Ulrich**; Schwede, Wolfgang; Skuballa, Werner; Buchmann, Bernd; Schirner, Michael
PATENT ASSIGNEE(S): Schering A.-G., Germany
SOURCE: Ger. Offen., 74 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19908767	A1	20001019	DE 1999-19908767	19990218

OTHER SOURCE(S): MARPAT 133:309795
GI



I



II

AB New epothilone derivs. I (R1a,R1b = R2a,R2b = same or different H, alkyl, aryl, aralkyl or (CH2)m,n m, n = 2-5; R3 = H, alkyl, aryl, aralkyl; R4a,R4b = same or different H, alkyl, aryl, aralkyl or (CH2)p = 2-5, CH2CH2, CH=CH, C≡C, epoxy, CH(OH)CH(OH), CH(OH)CH2; D-E = a group; R5 = H, alkyl, aryl, aralkyl; R6,R7 = H, bond, O; R8 = H, alkyl, aryl, aralkyl; X = O, OR23 alkylene-α,-ω-dioxy group straight or branched, OR9 or the CR10R11 group where R23 = alkyl, R9 = H or protecting group and R10,R11 = same or different H, alkyl, aryl, aralkyl or R10,R11 = together with methylene are a 5-7 membered carbocyclic ring; Y = O or two H; Z = O or H/OR12 and R12 = H or a protecting group) were prepd. Thus E- and Z-II were prepd. via a multistep synthesis. I cooperate with tubulin by stabilizing formed microtubuli. I are able phasespecifically to affect the cell division and are suitable for the treatment of malignant ovarian, stomach, colon, adeno, breast, lung, head and neck tumors, malignant melanomas, acute lymphocytic and myelocytic leukemia. Derivs. of I are suitable for use in anti-angiogenic therapy as well as for treating chronic inflammatory diseases (psoriasis, arthritis). In order to prevent uncontrolled cell proliferations and to improve the compatibility of medical implants I can be applied or incorporated into polymeric

materials. I can be used alone or to achieve additive or synergistic effects in combination with further principles and substance classes applicable in tumor therapy.

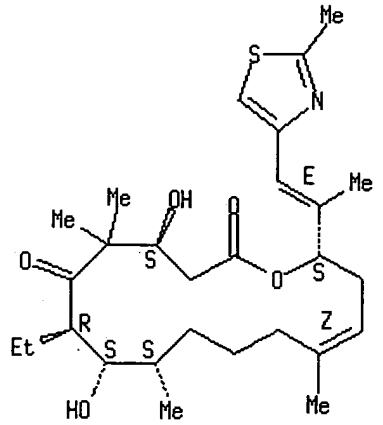
IT **220773-43-3P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of new epothilone derivs. and their pharmaceutical uses)

RN 220773-43-3 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 7-ethyl-4,8-dihydroxy-5,5,9,13-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



L10 ANSWER 5 OF 6 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

ACCESSION NUMBER: 2000:15195 HCAPLUS
DOCUMENT NUMBER: 132:64110
TITLE: The preparation process, intermediate products and pharmaceutical use of epothilone derivatives
INVENTOR(S): Buchmann, Bernd; **Klar, Ulrich**; Skuballa, Werner; Schwede, Wolfgang; Schirner, Michael; Menrad, Andreas
PATENT ASSIGNEE(S): Schering A.-G., Germany
SOURCE: PCT Int. Appl., 86 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000000485	A1	20000106	WO 1999-EP4915	19990630
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
DE 19830060	A1	20000210	DE 1998-19830060	19980630
DE 19923001	A1	20001116	DE 1999-19923001	19990513
AU 9950369	A1	20000117	AU 1999-50369	19990630

PRIORITY APPLN. INFO.: DE 1998-19830060 A 19980630
DE 1999-19923001 A 19990513
WO 1999-EP4915 W 19990630

OTHER SOURCE(S): CASREACT 132:64110; MARPAT 132:64110

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

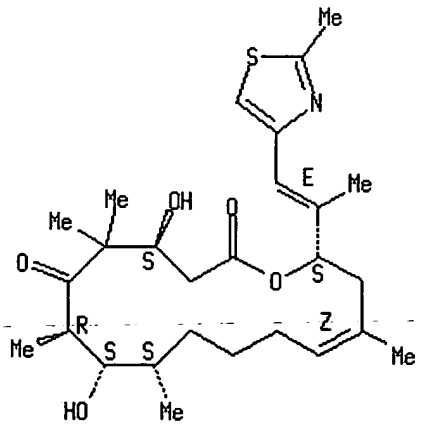
AB The invention relates to new epothilone derivs. I [R1a, R1b = H, C1-10-alkyl, aryl, C7-10-aralkyl; R1aR1b = (CH2)m, m = 2 - 5; R2a, R2b = H, C1-10-alkyl, aryl, C7-10-aralkyl; R2aR2b = (CH2)n, n = 2 - 5; R3 = H, C1-10-alkyl, aryl, C7-10-aralkyl; R4a, R4b = H, C1-10-alkyl, aryl, C7-10-aralkyl; R4aR4b = (CH2)m, m = 2 - 5; D-E = CH2CH2, CH:CH, C≡C, oxirane ring, CH(OH)CH(OH), CH(OH)CH2; R5 = C1-10-alkyl, aryl, C7-10-aralkyl; R6, R7 = H; R6R7 = O, bond; R8 = C1-10-alkyl, aryl, C7-10-aralkyl; R25 = H, C1-10-alkyl, C1-10-hydroxyalkyl, C1-10-haloalkyl; X = O, (OR9)2, C2-10-alkylene-α,ω-dioxy, CR11R12; CX = CH(OR10); R9 = C1-20-alkyl; R10 = H, protecting group; R11, R12 = H, C1-10-alkyl, aryl, C7-10-aralkyl; R11R12 = CH2, C5-7-carbocyclic ring; Y = O, CY = CH2; CZ = CH(OR13), R13 = H, protecting group] which are prepd. via cyclization of ketones II [R15 = H, OH halogen, OR15a, OSO2R15b; R15a = H, SO2-alkyl, SO2-aryl, SO2-aralkyl, (CH2)o, CR16aR16b; R15b = H, C1-20-alkyl, aryl, C7-20-aralkyl; R16a, R16b = H, C1-10-alkyl, aryl, C7-20-aralkyl; R16aR16b = (CH2)q; o = 2 - 4; q = 3 - 6]. Thus, epothilone deriv. III was prepd. via macrolactonization of carboxylic acid IV with 2,4,6-trichlorobenzoyl chloride and Et3N in THF followed by deprotection with aq. CF3CO2H in CH2Cl2. I cooperate with tubulin by stabilizing formed microtubuli.

IT **253447-39-1P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. and pharmaceutical use of epothilone derivs.)

RN 253447-39-1 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9,14-pentamethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 6 OF 6 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

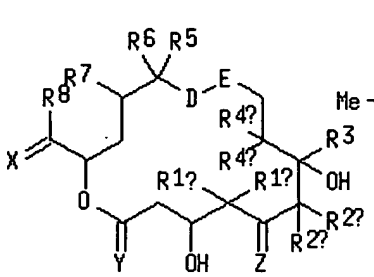
ACCESSION NUMBER: 1999:126888 HCAPLUS
DOCUMENT NUMBER: 130:196529
TITLE: Preparation of new epothilone derivatives as pharmaceutical agents
INVENTOR(S): **Klar, Ulrich**; Schwede, Wolfgang; Skuballa, Werner; Buchmann, Bernd; Schirner, Michael
PATENT ASSIGNEE(S): Schering Aktiengesellschaft, Germany
SOURCE: PCT Int. Appl., 185 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9907692	A2	19990218	WO 1998-EP5064	19980810
WO 9907692	A3	19990514		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DK, EE, ES, FI, GB, GE, GH, GM, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
DE 19735574	A1	19990211	DE 1997-19735574	19970809
DE 19735575	A1	19990211	DE 1997-19735575	19970809
DE 19735578	A1	19990211	DE 1997-19735578	19970809
DE 19748928	A1	19990429	DE 1997-19748928	19971024
DE 19749717	A1	19990506	DE 1997-19749717	19971031
DE 19751200	A1	19990520	DE 1997-19751200	19971113
DE 19813821	A1	19990923	DE 1998-19813821	19980320
AU 9893409	A1	19990301	AU 1998-93409	19980810
EP 1005465	A2	20000607	EP 1998-946309	19980810
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2001512723	T2	20010828	JP 2000-506196	19980810
ZA 9810403	A	20000515	ZA 1998-10403	19981113

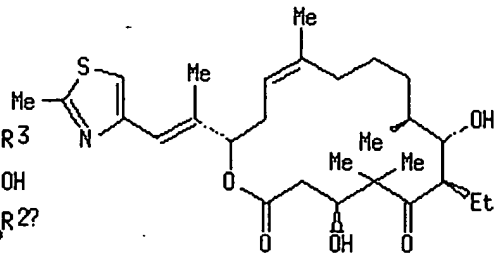
PRIORITY APPLN. INFO.:

DE 1997-19735574	A	19970809
DE 1997-19735575	A	19970809
DE 1997-19735578	A	19970809
DE 1997-19748928	A	19971024
DE 1997-19749717	A	19971031
DE 1997-19751200	A	19971113
DE 1998-19813821	A	19980320
WO 1998-EP5064	W	19980810

OTHER SOURCE(S): MARPAT 130:196529
GI



I



II

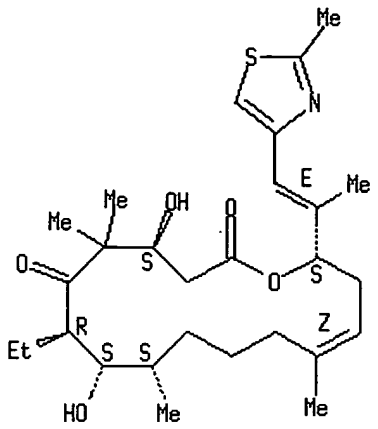
AB Epothilone derivs. of formula I [X = O, alkylene-α,ω-dioxy, two alkoxy groups, etc.; Y = O, H2; Z = O, (H, OH), (H, protected OH); R1a, R1b = H, alkyl, aryl, aralkyl, or together = (CH2)m where m = 2, 3, 4, 5; R2a, R2b = H, alkyl, aryl, aralkyl, or together = (CH2)n where n = 2, 3, 4, 5; when D-E = CH2CH2 or when Y = O, R2a or R2b may not be H/Me; R3 = H, alkyl, aryl, aralkyl; R4a, R4b = H, alkyl, aryl, aralkyl, or together = (CH2)p where p = 2, 3, 4, 5; D-E = CH2CH2, CH:CH, C≡C, 2,3-oxiranediyl, CH(OH)CH(OH), CH(OH)CH2; R5 = H, alkyl, aryl, aralkyl; R6, R7 = H, together = a satd. bond or O; R8 = H, alkyl, aryl, aralkyl all of which may be substituted] are prepd. Thus, the title compds. (4S,7R,8S,9S,13E,16S(E))- and (4S,7R,8S,9S,13Z,16S(E))-4,8-dihydroxy-7-ethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,13-tetramethylcyclohexadec-13-en-2,6-dione (II) were prepd. in many steps. The new compds. interact with tubulin by stabilizing formed microtubuli. They are capable of influencing cell division in a phase-specific manner and are suitable for the treatment of malignant tumors, such as ovarian, gastric, colon, breast, lung, head and neck carcinoma, adenocarcinoma, malignant melanoma, and acute lymphocytic and myelocytic leukemia. They are also suited for anti-angiogenesis therapy and for the treatment of chronic inflammatory diseases (psoriasis, arthritis). To prevent uncontrolled cell growth on, and for better tolerability of, medical implants, the derivs. can be introduced into or applied to polymeric materials. The compds. provided for in the invention can be used alone or, to achieve additive or synergistic effects, in combination with other principles and substance categories used in tumor therapy.

IT **220773-43-3P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of epothilone derivs. as antitumor agents)

RN 220773-43-3 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 7-ethyl-4,8-dihydroxy-5,5,9,13-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.




```
=> d his

     (FILE 'HOME' ENTERED AT 16:57:10 ON 22 AUG 2002)

     FILE 'REGISTRY' ENTERED AT 16:57:18 ON 22 AUG 2002
L1             STRUCTURE UPLOADED
L2              11 S L1
L3             235 S L1 FULL

     FILE 'HCAPLUS' ENTERED AT 17:02:57 ON 22 AUG 2002
L4             134 S L3

     FILE 'REGISTRY' ENTERED AT 17:03:04 ON 22 AUG 2002
L5             STRUCTURE UPLOADED
L6               8 S L5
L7             121 S L5 FULL

     FILE 'HCAPLUS' ENTERED AT 17:07:15 ON 22 AUG 2002
L8             132 S L7
L9              34 S L8 AND PD < SEPTEMBER 1998
L10              6 S L8 AND KLAR, U?/AU
L11              0 S L9 AND KLAR, U?/AU

=> s l9 not l10
L12            34 L9 NOT L10

=> d l12, ibib abs fhitstr, 1-34

L12  ANSWER 1 OF 34  HCAPLUS  COPYRIGHT 2002 ACS
```

Full Text | Citing References

```
ACCESSION NUMBER:         2000:316343  HCAPLUS
                            Correction of: 1997:528752
DOCUMENT NUMBER:          132:293587
                            Correction of: 127:149021
TITLE:                    The Olefin Metathesis Approach to Epothilone A and Its
                          Analogs
AUTHOR(S):                Nicolaou, K. C.; He, Y.; Vourloumis, D.; Vallberg, H.;
                          Roschangar, F.; Sarabia, F.; Ninkovic, S.; Yang, Z.;
                          Trujillo, J. I.
CORPORATE SOURCE:         Institute for Chemical Biology, La Jolla, CA, 92037,
                          USA
SOURCE:                   Journal of the American Chemical Society (1997),
                          119(34), 7960-7973
                          CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER:                American Chemical Society
DOCUMENT TYPE:            Journal
```

LANGUAGE: English
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

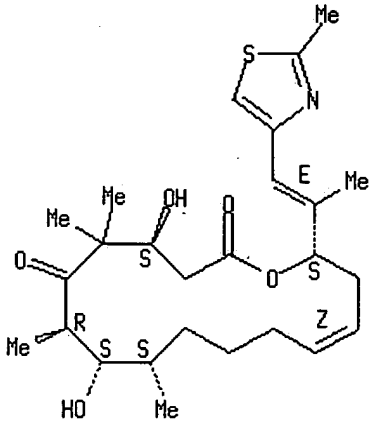
AB The olefin metathesis approach to epothilone A (I) and several diastereomeric analogs is described. Key building blocks II, (S)-OHCCH(Me)CH2CH2CH2CH=CH2, and (S)-MeCH2COC(Me)2CH(OSiMe2CMe3)CH2CO2H were constructed in optically active form and were coupled and elaborated to olefin metathesis precursor III (R = SiMe2CMe3) via an aldol reaction and an esterification coupling. Olefin metathesis of compd. III (R = SiMe2CMe3), under the catalytic influence of RuCl2(:CHPh)(PCy3)2, furnished cis- and trans-cyclic olefins IV (R = SiMe2CMe3). Epoxidn. of (Z)-IV (R = H) gave I and several analogs, whereas epoxidn. of (E)-IV (R = H) resulted in addnl. epothilones. Similar elaboration of isomeric as well as simpler intermediates resulted in yet another series of epothilone analogs and model systems.

IT **186692-73-9P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis of epothilone A and analogs via olefin metathesis)

RN 186692-73-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L12 ANSWER 2 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

ACCESSION NUMBER: 1999:19340 HCAPLUS
DOCUMENT NUMBER: 130:217758
TITLE: Desoxyepothilone B is curative against human tumor xenografts that are refractory to paclitaxel
AUTHOR(S): Chou, Ting-Chao; Zhang, Xiu-Guo; Harris, Christina R.; Kuduk, Scott D.; Balog, Aaron; Savin, Kenneth A.; Bertino, Joseph R.; Danishefsky, Samuel J.
CORPORATE SOURCE: Molecular Pharmacology and Therapeutics Program, Sloan-Kettering Institute for Cancer Research, New York, NY, 10021, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (**1998**), 95(26), 15798-15802
CODEN: PNASA6; ISSN: 0027-8424

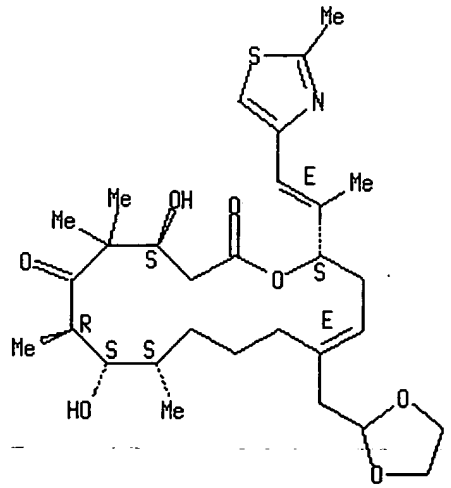
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The epothilones are naturally occurring, cytotoxic macrolides that function through a paclitaxel (Taxol)-like mechanism. Although structurally dissimilar, both classes of mols. lead to the arrest of cell division and eventual cell death by stabilizing cellular microtubule assemblies. The epothilones differ in their ability to retain activity against multidrug-resistant (MDR) cell lines and tumors where paclitaxel fails. In the current account, we focus on the relationship between epothilone and paclitaxel in the context of tumors with multiple drug resistance. The epothilone analog Z-12,13-desoxyepothilone B (dEpoB) is >35,000-fold more potent than paclitaxel in inhibiting cell growth in the MDR DC-3F/ADX cell line. Various formulations, routes, and schedules of i.v. administration of dEpoB have been tested in nude mice. Slow infusion with a Cremophor-ethanol vehicle proved to be the most beneficial in increasing efficacy and decreasing toxicity. Although dEpoB performed similarly to paclitaxel in sensitive tumors xenografts (MX-1 human mammary and HT-29 colon tumor), its effects were clearly superior against MDR tumors. When dEpoB was administered to nude mice bearing our MDR human lymphoblastic T cell leukemia (CCRF-CEM/paclitaxel), dEpoB demonstrated a full curative effect. For human mammary adenocarcinoma MCF-7/Adr cells refractory to paclitaxel, dEpoB reduced the established tumors, markedly suppressed tumor growth, and surpassed other commonly used chemotherapy drugs such as adriamycin, vinblastine, and etoposide in beneficial effects.

IT **198475-07-9**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(antitumor activity of desoxyepothilone B analogs)

RN 198475-07-9 HCAPLUS
CN Oxacyclohexadec-13-ene-2,6-dione, 13-(1,3-dioxolan-2-ylmethyl)-4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13E,16S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 3 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

ACCESSION NUMBER: 1998:805542 HCAPLUS
DOCUMENT NUMBER: 130:153488

TITLE: The antibody catalysis route to the total synthesis of epothilones

AUTHOR(S): Sinha, Subhash C.; Barbas, Carlos F., III; Lerner, Richard A.

CORPORATE SOURCE: The Skaggs Institute for Chemical Biology and the Department of Molecular Biology, The Scripps Research Institute, La Jolla, CA, 92037, USA

SOURCE: Proceedings of the National Academy of Sciences of the United States of America (**1998**), 95(25), 14603-14608
CODEN: PNASA6; ISSN: 0027-8424

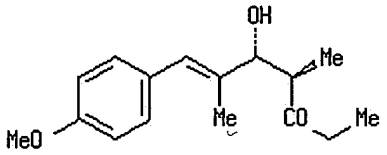
PUBLISHER: National Academy of Sciences

DOCUMENT TYPE: Journal

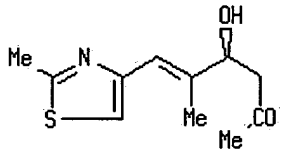
LANGUAGE: English

OTHER SOURCE(S): CASREACT 130:153488

GI



I



II

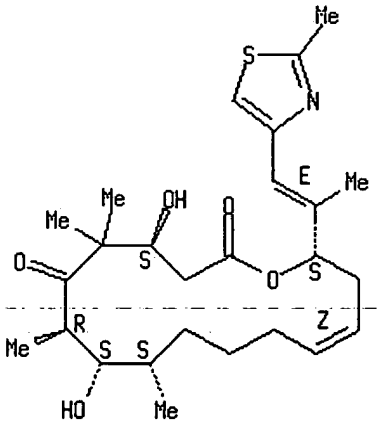
AB A total synthesis of epothilones A and C via antibody-catalyzed aldol and retro-aldol reactions was described. Epothilone precursors (+)-I and (-)-II were prepd. using aldolase antibody 38C2 as a catalyst. These precursors were then converted to epothilones A and C to complete the total synthesis.

IT **186692-73-9P**, Epothilone C
RL: BPN (Biosynthetic preparation); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(total synthesis of epothilones via antibody 38C2 catalyzed retro-aldol reactions)

RN 186692-73-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



REFERENCE COUNT: 62 THERE ARE 62 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 4 OF 34 HCAPLUS COPYRIGHT 2002 ACS

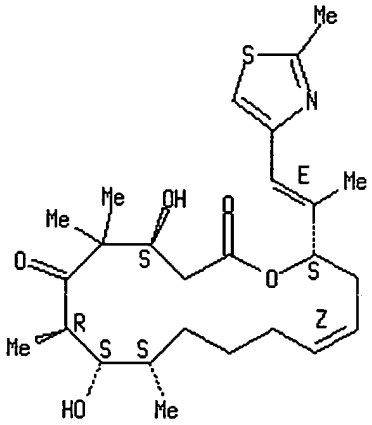
Full Text | Citing References

ACCESSION NUMBER: 1998:760826 HCAPLUS
DOCUMENT NUMBER: 130:95407
TITLE: Derivatization of the C12-C13 functional groups of epothilones A, B and C
AUTHOR(S): Sefkow, Michael; Kiffe, Michael; Hofle, Gerhard
CORPORATE SOURCE: Gesellschaft fur Biotechnologische Forschung mbH, Abt. Naturstoffchemie, Braunschweig, D-38124, Germany
SOURCE: Bioorganic & Medicinal Chemistry Letters (**1998**), 8(21), 3031-3036
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 130:95407

AB Epothilone A reacted with hydrohalic acids to give C12-C13 halohydrin regioisomers (ratios: 2:1 - 4:1), whereas epothilone B gave under the same conditions the isomerically pure C12 halo C13 hydroxy deriv. With non-nucleophilic Bronstedt acids and with Lewis acids a highly solvent dependent product distribution and some unexpected rearrangement products were obsd. Epothilone C bearing a double bond between C12 and C13 was regioselectively dihydroxylated or hydrogenated at that position.

IT **186692-73-9**, Epothilone C
RL: RCT (Reactant); RACT (Reactant or reagent)
(derivatization of the C12-C13 functional groups of epothilones A, B and C)
RN 186692-73-9 HCAPLUS
CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

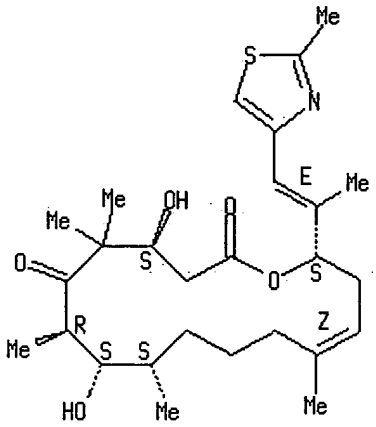
L12 ANSWER 5 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

ACCESSION NUMBER: 1998:732784 HCAPLUS
DOCUMENT NUMBER: 130:81320
TITLE: Easy access to the epothilone family - synthesis of epothilone B
AUTHOR(S): Mulzer, Johann; Mantoulidis, Andreas; Ohler, Elisabeth
CORPORATE SOURCE: Inst. fur Organische Chemie, Univ. Wien, Vienna, A-1090, Austria
SOURCE: Tetrahedron Letters (**1998**), 39(47), 8633-8636
CODEN: TELEAY; ISSN: 0040-4039
PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 130:81320
AB An easy access to four out of five naturally occurring epothilones (A-E) is reported. Key steps are an enantioselective Mukaiyama type aldol reaction, (E)- and (Z)-selective olefinations, and a sulfone alkylation.
IT **189453-10-9P**, Epothilone D
RL: SPN (Synthetic preparation); PREP (Preparation)
(synthesis of epothilone B)
RN 189453-10-9 HCAPLUS
CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.

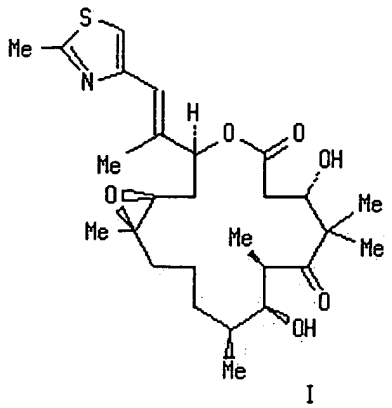


REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

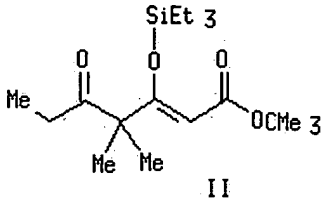
L12 ANSWER 6 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

ACCESSION NUMBER: 1998:726876 HCAPLUS
DOCUMENT NUMBER: 130:81319
TITLE: A novel aldol condensation with 2-methyl-4-pentenal and its application to an improved total synthesis of epothilone B
AUTHOR(S): Balog, Aaron; Harris, Christina; Savin, Kenneth; Zhang, Xiu-Guo; Chou, Ting Chao; Danishefsky, Samuel J.
CORPORATE SOURCE: Laboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, New York, NY, 10021, USA
SOURCE: Angewandte Chemie, International Edition (**1998**), 37(19), 2675-2678
CODEN: ACIEF5; ISSN: 1433-7851
PUBLISHER: Wiley-VCH Verlag GmbH
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 130:81319
GI



I



II

AB Epothilone B was prepd. in 9 steps via aldol condensation of (S)-2-methyl-4-pentenal with the enolate I.

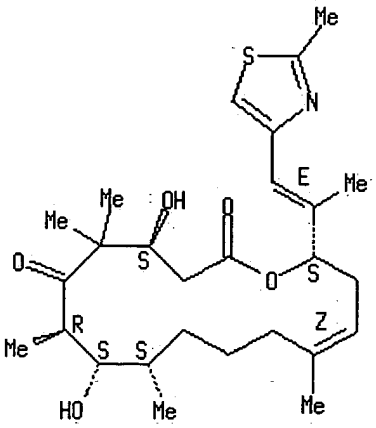
IT **189453-10-9P**

RL: SPN (Synthetic preparation); PREP (Preparation)
(novel aldol condensation with 2-methyl-4-pentenal and application to improved total synthesis of epothilone B)

RN 189453-10-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 7 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

ACCESSION NUMBER: 1998:534644 HCAPLUS
DOCUMENT NUMBER: 129:239597
TITLE: Desoxyepothilone B: an efficacious microtubule-targeted antitumor agent with a promising in vivo profile relative to epothilone B
AUTHOR(S): Chou, Ting-Chao; Zhang, Xiu-Guo; Balog, Aaron; Su, Dai-Shi; Meng, Dongfang; Savin, Kenneth; Bertino, Joseph R.; Danishefsky, Samuel J.
CORPORATE SOURCE: Molecular Pharmacology and Therapeutics Program, Cornell University Graduate School of Medical Sciences, New York, NY, 10021, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (**1998**), 95(16), 9642-9647

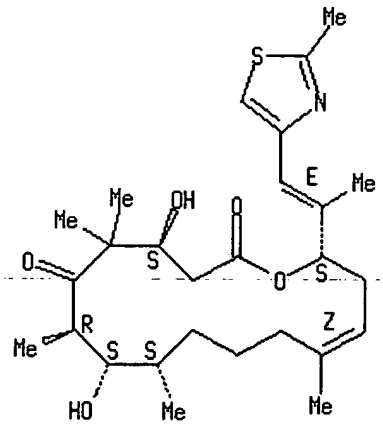
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A new class of 16-membered macrolides, the epothilones (Epos), has been synthesized and evaluated for antitumor potential in vitro and in vivo. Recent studies in these and other labs. showed that epothilones and paclitaxel (paclitaxel) share similar mechanisms of action in stabilizing microtubule arrays as indicated by binding-displacement studies, substitution for paclitaxel in paclitaxel-dependent cell growth, and electron microscopic examns. The present study examd. cell growth-inhibitory effects in two rodent and three human tumor cell lines and their drug-resistant sublines. Although paclitaxel showed as much as 1,970-fold cross-resistance to the sublines resistant to paclitaxel, adriamycin, vinblastine, or actinomycin D, most epothilones exhibit little or no cross-resistance. In multidrug-resistant CCRF-CEM/VBL100 cells, IC50 values for EpoA (1), EpoB (2), desoxyEpoA (3) (dEpoA), desoxyEpoB (4) (dEpoB), and paclitaxel were 0.02, 0.002, 0.012, 0.017, and 4.14 μM, resp. In vivo studies, using i.p. administration, indicated that the parent, EpoB, was highly toxic to mice and showed little therapeutic effect when compared with a lead compd., dEpoB. More significantly, dEpoB (25-40 mg/kg, Q2Dx5, i.p.) showed far superior therapeutic effects and lower toxicity than paclitaxel, doxorubicin, camptothecin, or vinblastine (at maximal tolerated doses) in parallel expts. For mammary adenocarcinoma xenografts resistant to adriamycin, MCF-7/Adr, superior therapeutic effects were obtained with dEpoB compared with paclitaxel when i.p. regimens were used. For ovarian adenocarcinoma xenografts, SK-OV-3, dEpoB (i.p.), and paclitaxel (i.v.) gave similar therapeutic effects. In nude mice bearing a human mammary carcinoma xenograft (MX-1), marked tumor regression and cures were obtained with dEpoB.

IT **189453-10-9**, Desoxyepothilone B
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(desoxyepothilone B is an efficacious microtubule-targeted antitumor agent with a promising in vivo profile relative to epothilone B)

RN 189453-10-9 HCAPLUS
CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L12 ANSWER 8 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

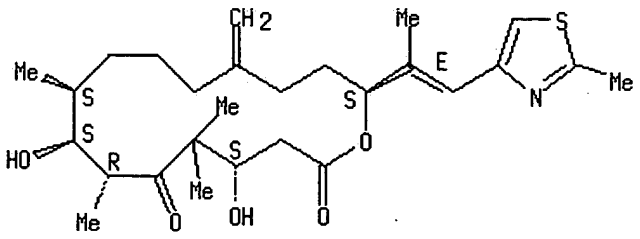
ACCESSION NUMBER: 1998:503765 HCAPLUS
DOCUMENT NUMBER: 129:244965
TITLE: Synthesis and biological properties of C12,13-cyclopropyl-epothilone A and related epothilones
AUTHOR(S): Nicolaou, K. C.; Finlay, M. Ray V.; Ninkovic, Sacha; King, N. Paul; He, Yun; Li, Tianhu; Sarabia, Francisco; Vourloumis, Dionisios
CORPORATE SOURCE: Dep. Chemistry, The Skaggs Inst. Chem. Biol., The Scripps Res. Inst., La Jolla, CA, 92037, USA
SOURCE: Chemistry & Biology (**1998**), 5(7), 365-372
CODEN: CBOLE2; ISSN: 1074-5521
PUBLISHER: Current Biology Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 129:244965

AB Background: The epothilones are natural substances that are potently cytotoxic, having an almost identical mode of action to Taxol as tubulin-polymn. and microtubule-stabilizing agents. The development of detailed structure-activity relationships for these compds. and the further elucidation of their mechanism of action is of high priority. Results: The chem. synthesis of the C12,13-cyclopropyl analog of epothilone A and its C12,13-trans-diastereoisomer has been accomplished. These compds. and several other epothilone analogs have been screened for their ability to induce tubulin polymn. and death of a no. of tumor cells. Several interesting structure-activity trends within this family of compds. were identified. Conclusions: The results of the biol. tests conducted in this study have demonstrated that, although a no. of positions on the epothilone skeleton are amenable to modification without significant loss of biol. activity, the replacement of the epoxide moiety of epothilone A with a cyclopropyl group leads to total loss of activity.

IT **213312-66-4**
RL: RCT (Reactant); RACT (Reactant or reagent)
(synthesis and biol. properties of C12,13-cyclopropyl-epothilone A and related epothilones)

RN 213312-66-4 HCAPLUS
CN Oxacyclohexadecane-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-13-methylene-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,16S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.

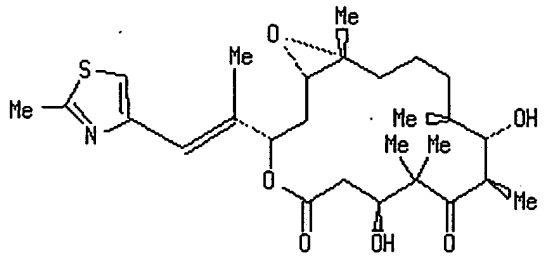


L12 ANSWER 9 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

ACCESSION NUMBER: 1998:492150 HCAPLUS
DOCUMENT NUMBER: 129:216449
TITLE: Total synthesis of (-)-epothilone B
AUTHOR(S): May, Scott A.; Grieco, Paul A.
CORPORATE SOURCE: Department of Chemistry and Biochemistry, Montana State University, Bozeman, MT, 59717, USA
SOURCE: Chemical Communications (Cambridge) (**1998**), (15), 1597-1598

CODEN: CHCOFS; ISSN: 1359-7345
PUBLISHER: Royal Society of Chemistry
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

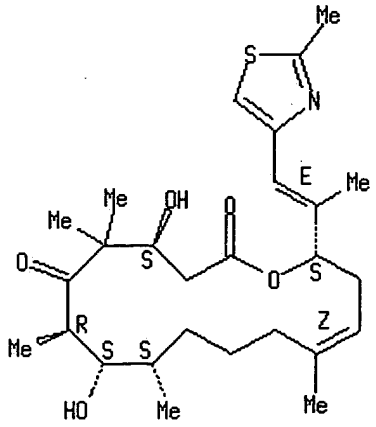
AB The sixteen-membered ring macrolide (-)-epothilone B (I) has been synthesized by a route which features stereospecific methylation of an (E)-γ,δ-epoxy acrylate, the use of a double asym. reaction employing (R,R)-diisopropyltartrate and (E)-crotylboronate, ring closure by means of an olefin metathesis reaction.

IT **189453-10-9P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(total synthesis of (-)-epothilone B)

RN 189453-10-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L12 ANSWER 10 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

ACCESSION NUMBER: 1998:405952 HCAPLUS
DOCUMENT NUMBER: 129:81625
TITLE: Preparation of epothilone analogs as anticancer agents
INVENTOR(S): Nicolaou, Costa Kyriacos; He, Yun; Ninkovic, Sacha; Pastor, Joaquin; Roschangar, Frank; Sarabia, Francisco; Vallberg, Hans; Vourloumis, Dionisios; Winssinger, Nicolas; Yang, Zhen; King, Nigel Paul; et al.
PATENT ASSIGNEE(S): Novartis A.-G., Switz.; Scripps Research Institute
SOURCE: PCT Int. Appl., 213 pp.

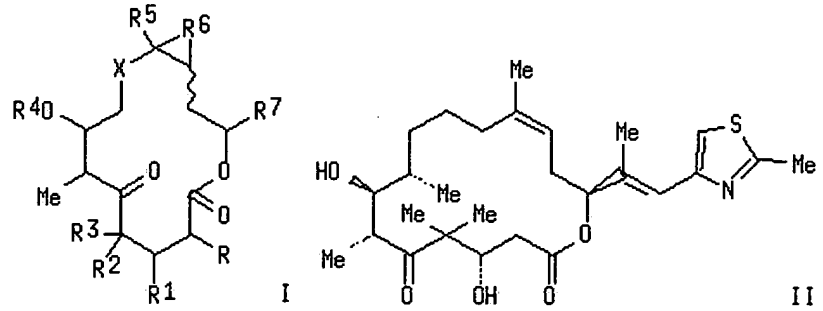
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9825929	**A1**	**19980618**	**WO 1997-EP7011**	**19971212**
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9857577	**A1**	**19980703**	**AU 1998-57577**	**19971212**
AU 746597	B2	20020502		
EP 944634	A1	19990929	EP 1997-953808	19971212
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 9714140	A	20000229	BR 1997-14140	19971212
CN 1246862	A	20000308	CN 1997-181771	19971212
JP 2001504856	T2	20010410	JP 1998-526247	19971212

PRIORITY APPLN. INFO.:

US 1996-32864P	P	19961213
US 1997-856533	A	19970514
US 1997-923869	A2	19970904
WO 1997-EP7011	W	19971212

OTHER SOURCE(S): MARPAT 129:81625
GI



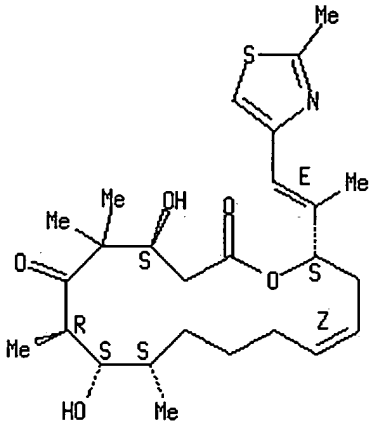
AB Epothilone A, epothilone B, analogs of epothilone and libraries of epothilone analogs of formula I [X = (CH2)n; n = 1-5; R1 = OH, OMe, absent; R2, R3 = H, CH2, Me; R4 = H, Me, protecting group; R5 = H, Me, CHO, (substituted) CO2H, etc.; R6 = O, CH2, absent; R7 = thiazolealkyl, etc.] are synthesized. Epothilone A and B are known anticancer agents that derive their anticancer activity by the prevention of mitosis through the induction and stabilization of microtubulin assembly. Several of the analogs are demonstrated to have a superior cytotoxic activity as compared to epothilone A or epothilone B as demonstrated by their enhanced ability to induce the polymn. and stabilization of microtubules. Thus, II was prepd. and was shown to induce tubulin polymn. at 94% relative to GTP, and inhibit carcinoma cell growth.

IT **186692-73-9P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of epothilone analogs as anticancer agents)

RN 186692-73-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

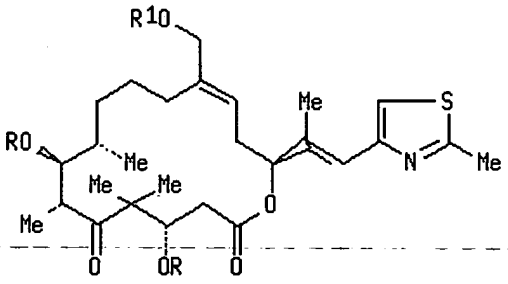
Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L12 ANSWER 11 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

ACCESSION NUMBER: 1998:378435 HCAPLUS
DOCUMENT NUMBER: 129:189151
TITLE: Total synthesis of 26-hydroxy-epothilone B and related analogs via a macrolactonization based strategy
AUTHOR(S): Nicolaou, K. C.; Finlay, M. Ray V.; Ninkovic, Sacha; Sarabia, Francisco
CORPORATE SOURCE: Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, La Jolla, CA, 92037, USA
SOURCE: Tetrahedron (**1998**), 54(25), 7127-7166
CODEN: TETRAB; ISSN: 0040-4020
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 129:189151
GI



I

AB The chem. synthesis of a series of 26-substituted epothilones B was described. Fully protected 26-hydroxydesoxy-epothilone B I (R = SiMe2CMe3, R1 = CPh3), prepd. via a macrolactonization strategy, served as a common precursor to the designed epothilones described. The synthesized compds. were members of a large epothilone library of a no. of antitumor agents.

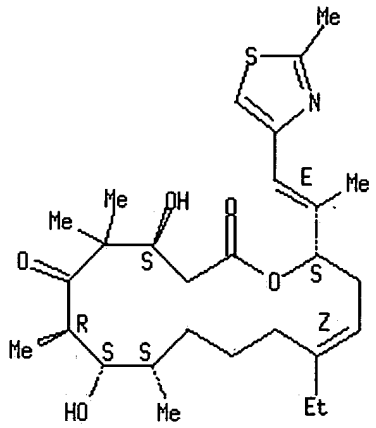
IT **198475-04-6P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT

(Reactant or reagent)
(total synthesis of 26-hydroxy-epothilone B and related analogs via a macrolactonization based strategy)

RN 198475-04-6 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 13-ethyl-4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L12 ANSWER 12 OF 34 HCAPLUS COPYRIGHT 2002 ACS

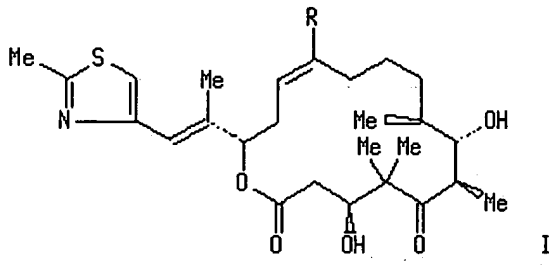
Full Text | Citing References

ACCESSION NUMBER: 1998:352834 HCAPLUS
DOCUMENT NUMBER: 129:53436
TITLE: Epothilone C, D, E and F, production process, and their use as cytostatics well as phytosanitary agents
INVENTOR(S): Reichenbach, Hans; Hofle, Gerhard; Gerth, Klaus; Steinmetz, Heinrich
PATENT ASSIGNEE(S): Gesellschaft Fur Biotechnologische Forschung m.b.H. (GBF), Germany; Reichenbach, Hans; Hofle, Gerhard; Gerth, Klaus; Steinmetz, Heinrich
SOURCE: PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

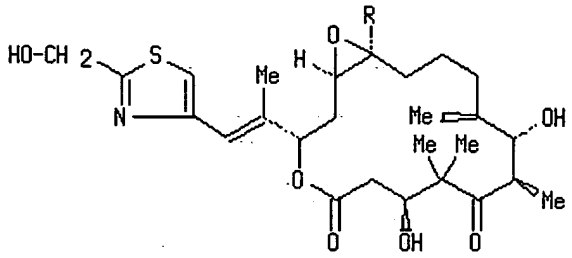
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9822461	**A1**	**19980528**	**WO 1997-EP6442**	**19971118**
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9854837	**A1**	**19980610**	**AU 1998-54837**	**19971118**
ZA 9710384	A	19990518	ZA 1997-10384	19971118
EP 941227	A1	19990915	EP 1997-951233	19971118
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
CN 1237970	A	19991208	CN 1997-199814	19971118
BR 9713363	A	20000125	BR 1997-13363	19971118

JP 2001504474	T2	20010403	JP 1998-523208		19971118
TW 408119	B	20001011	TW 1997-86117334		19980121
NO 9902338	A	19990514	NO 1999-2338		19990514
KR 2000053308	A	20000825	KR 1999-704302		19990514
PRIORITY APPLN. INFO.:			DE 1996-19647580	A	19961118
			DE 1997-19707506	A	19970225
			WO 1997-EP6442	W	19971118

GI



I



II

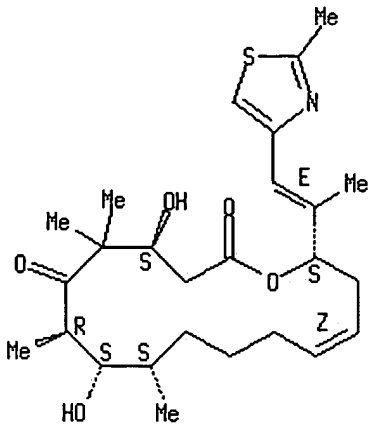
AB The present invention concerns the epothilones, esp. epothilone C [I; R = H] and epothilone D [I; R = Me] as well as epothilone E [II; R = H] and epothilone F [II; R = Me], the prodn. process, and their application for producing therapeutic agents, including cytostatic agents as well as phytosanitary agents.

IT **186692-73-9P**, Epothilone C
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(epothilone C, D, E and F, prodn. process, and use as cytostatics well as phytosanitary agents)

RN 186692-73-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L12 ANSWER 13 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

ACCESSION NUMBER: 1998:163596 HCAPLUS
DOCUMENT NUMBER: 128:217229
TITLE: Method for producing epothilones and the intermediate products obtained during the production process
INVENTOR(S): Schinzer, Dieter; Limberg, Anja; Bohm, Oliver M.; Bauer, Armin; Cordes, Martin
PATENT ASSIGNEE(S): Novartis Aktiengesellschaft, Switz.; Schinzer, Dieter; Limberg, Anja; Bohm, Oliver M.; Bauer, Armin; Cordes, Martin
SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9808849	**A1**	**19980305**	**WO 1997-DE111**	**19970115**
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
DE 19636343	**C1**	**19971023**	**DE 1996-19636343**	**19960830**
DE 19645361	**A1**	**19980430**	**DE 1996-19645361**	**19961028**
DE 19645362	**A1**	**19980430**	**DE 1996-19645362**	**19961028**
AU 9721493	**A1**	**19980319**	**AU 1997-21493**	**19970115**
AU 716610	B2	20000302		
EP 923583	A1	19990623	EP 1997-914077	19970115
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2001500851	T2	20010123	JP 1998-511141	19970115

PRIORITY APPLN. INFO.:
DE 1996-19636343 A 19960830
DE 1996-19645361 A 19961028
DE 1996-19645362 A 19961028
WO 1997-DE111 W 19970115

OTHER SOURCE(S): CASREACT 128:217229; MARPAT 128:217229
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

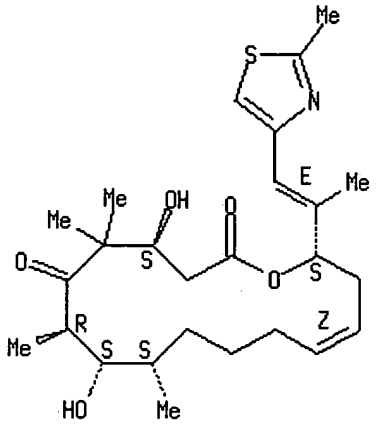
AB A method for producing epothilones I [R = H (A), Me (B)] is characterized by reaction of thiazole II with carboxylic acid III (B = CH2Ph, THP, silyl protecting group; R = H, Me), followed by olefin metathesis in the presence of a noble metal catalyst, hydroxyl deprotection and epoxidn. Thus, epothilone A (I; R = H) was prepd. via acylation of II with III (R = H, B = SiMe2CMe3) in CH2Cl2 contg. DCC and DMAP, followed by olefin metathesis in CH2Cl2 contg. catalytic benzylidenebis(tricyclohexylphosphine)ruthenium dichloride, desilylation with aq. HF in Et2O/MeCN and epoxidn. with dimethyldioxirane in acetone. Epothilones A and B are natural substances which are produced by microorganisms and have similar properties to those of taxol and, therefore, are of interest to the pharmaceutical chem.

IT **186692-73-9P**, Epothilone C
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of epothilones via olefin metathesis)

RN 186692-73-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L12 ANSWER 14 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

ACCESSION NUMBER: 1998:121923 HCAPLUS
DOCUMENT NUMBER: 128:252599
TITLE: Farnesyl transferase inhibitors cause enhanced mitotic sensitivity to taxol and epothilones
AUTHOR(S): Moasser, Mark M.; Sepp-Lorenzino, Laura; Kohl, Nancy E.; Oliff, Allen; Balog, Aaron; Su, Dai-Shi; Danishefsky, Samuel J.; Rosen, Neal
CORPORATE SOURCE: Department of Medicine, Memorial Sloan-Kettering Cancer Center, Sloan-Kettering Institute, New York, NY, 10021, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (**1998**), 95(4), 1369-1374
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB An important class of cellular proteins, which includes members of the p21ras family, undergoes post-translational farnesylation, a modification

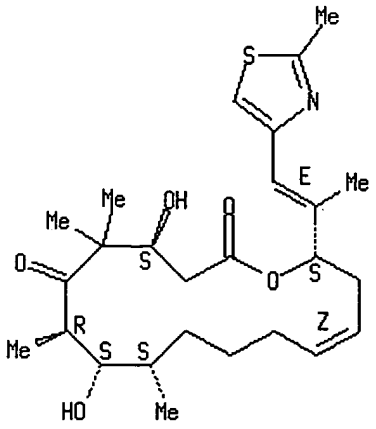
required for their partition to membranes. Specific farnesyl transferase inhibitors (FTIs) have been developed that selectively inhibit the processing of these proteins. FTIs have been shown to be potent inhibitors of tumor cell growth in cell culture and in murine models and at doses that cause little toxicity to the animal. These data suggest that these drugs might be useful therapeutic agents. We now report that, when FTI is combined with some cytotoxic antineoplastic drugs, the effects on tumor cells are additive. No interference is noted. Furthermore, FTI and agents that prevent microtubule depolymn., such as taxol or epothilones, act synergistically to inhibit cell growth. FTI causes increased sensitivity to induction of metaphase block by these agents, suggesting that a farnesylated protein may regulate the mitotic check point. The findings imply that FTI may be a useful agent for the treatment of tumors with wild-type ras that are sensitive to taxanes.

IT **186692-73-9**, Desoxyepothilone A
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(farnesyl transferase inhibitors cause enhanced mitotic sensitivity to taxol and epothilones)

RN 186692-73-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.

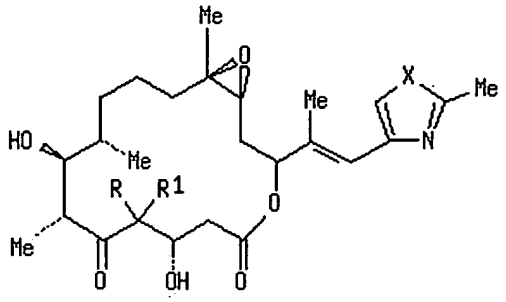


103

L12 ANSWER 15 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

ACCESSION NUMBER: 1998:50907 HCAPLUS
DOCUMENT NUMBER: 128:180246
TITLE: Total synthesis of oxazole- and cyclopropane-containing epothilone B analogs by the macrolactonization approach
AUTHOR(S): Nicolaou, K. C.; Sarabia, Francisco; Finlay, M. Ray V.; Ninkovic, Sacha; King, N. Paul; Vourloumis, Dionisios; He, Yun
CORPORATE SOURCE: Department of Chemistry and The Skaggs Institute for Chemical Biology The Scripps Research Institute, La Jolla, CA, 92037, USA
SOURCE: Chemistry--A European Journal (**1997**), 3(12), 1971-1986
CODEN: CEUJED; ISSN: 0947-6539
PUBLISHER: Wiley-VCH Verlag GmbH
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

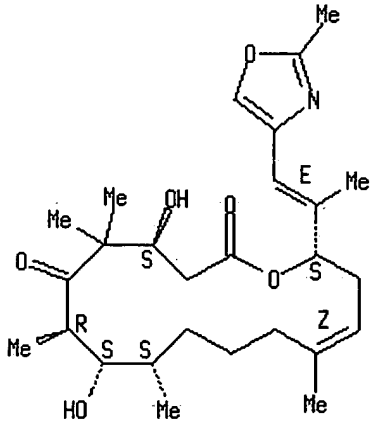
AB In order to probe structure-activity relationships in the epothilone area, two series of epothilone B analogs were designed and synthesized. The first series contg. an oxazole moiety in place of a thiazole on the side chain was constructed via utilization of key intermediates whereas the second series contg. an ethano group instead of the gem-di-Me group at position 4 was synthesized. A Yamaguchi-type macrolactonization reaction was used to construct the macrocycle from a secoacid, which was assembled, in both cases, via a) an aldol reaction, b) an Enders alkylation, and c) a Wittig-type reaction. This convergent strategy provided access to oxazole and 4,4-ethano analogs, e.g., I (R = R1 = Me, X = O, S; RR1 = CH2CH2, X = O, S).

IT **198571-09-4P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(total synthesis of oxazole- and cyclopropane-contg. epothilone B analogs via macrolactonization)

RN 198571-09-4 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-[(1E)-1-methyl-2-(2-methyl-4-oxazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



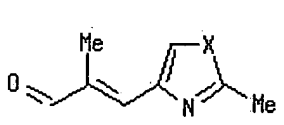
10 2

L12 ANSWER 16 OF 34 HCAPLUS COPYRIGHT 2002 ACS

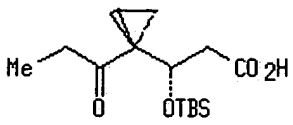
Full Text | Citing References

ACCESSION NUMBER: 1998:50906 HCAPLUS
DOCUMENT NUMBER: 128:140541
TITLE: Total synthesis of oxazole- and cyclopropane-containing epothilone A analogs by the olefin metathesis approach
AUTHOR(S): Nicolaou, K. C.; Vallberg, Hans; King, N. Paul; Roschangar, Frank; He, Yun; Vourloumis, Dionisios;

Nicolaou, Christopher G.
CORPORATE SOURCE: Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, La Jolla, CA, 92037, USA
SOURCE: Chemistry--A European Journal (**1997**), 3(12), 1957-1970
CODEN: CEUJED; ISSN: 0947-6539
PUBLISHER: Wiley-VCH Verlag GmbH
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I



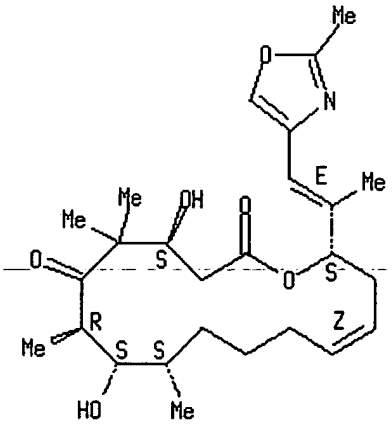
III

AB For structure-activity relationship studies, two series of epothilone A analogs have been designed and synthesized, one contg. an oxazole moiety instead of the thiazole heterocycle and the other contg. a spirocyclopropane moiety in place of the gem-di-Me group at position C-4 (4,4-ethano-epothilones). The olefin metathesis strategy in soln. was utilized for the chem. synthesis of these compds. starting with key building blocks (I) (X = O), (S)-H2C=CH(CH2)3CH(Me)CHO (II), (S)-MeCH2COCMe2CH(OSiMe2CMe3)CH2CO2H for the oxazole series and building blocks I (X = S), II, and (III) for the 4,4-ethano series. The convergent strategy towards the designed epothilone A series involved: a- an aldol condensation reaction, b- an esterification reaction, c- an olefin metathesis reaction catalyzed by [RuCl2(=CHPh)-(PCy3)2], and d- epoxidn. of the macrocycle double bond.

IT **198475-12-6P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(total synthesis of oxazole- and cyclopropane-contg. epothilone A analogs by the olefin metathesis approach)

RN 198475-12-6 HCAPLUS
CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-oxazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L12 ANSWER 17 OF 34 HCAPLUS COPYRIGHT 2002 ACS

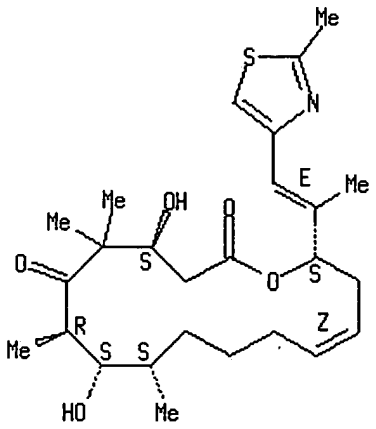
Full Text | Citing References

ACCESSION NUMBER: 1998:729 HCAPLUS
DOCUMENT NUMBER: 128:88685
TITLE: Metathesis vs metastasis: the chemistry and biology of the epothilones
AUTHOR(S): Finlay, Ray
CORPORATE SOURCE: Dep. Chemistry, The Skaggs Inst. for Chemical Biol., The Scripps Res. Inst., La Jolls, CA, 92037, USA
SOURCE: Chemistry & Industry (London) (**1997**), (24), 991-996
CODEN: CHINAG; ISSN: 0009-3068
PUBLISHER: Society of Chemical Industry
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 15 refs. on a recent entry onto the scene of potentially useful natural products, the epothilones A - E, providing valuable information for the fight against cancer via their interaction with microtubules.

IT **186692-73-9P**, Epothilone C
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation); USES (Uses)
(chem. and bioactivity of the epothilones)
RN 186692-73-9 HCAPLUS
CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.

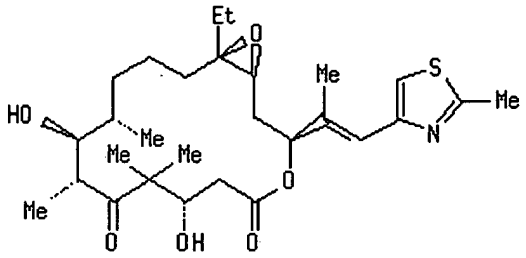


L12 ANSWER 18 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

ACCESSION NUMBER: 1997:787450 HCAPLUS
DOCUMENT NUMBER: 128:101936
TITLE: Total synthesis of 26-hydroxyepothilone B and related analogs
AUTHOR(S): Nicolaou, K. C.; Ninkovic, Sacha; Finlay, M. Ray V.; Sarabia, Francisco; Li, Tianhu
CORPORATE SOURCE: Department of Chemistry and Biochemistry, University of California, California, 92093, USA
SOURCE: Chemical Communications (Cambridge) (**1997**), (24), 2343-2344
CODEN: CHCOFS; ISSN: 1359-7345
PUBLISHER: Royal Society of Chemistry
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 128:101936

GI



I

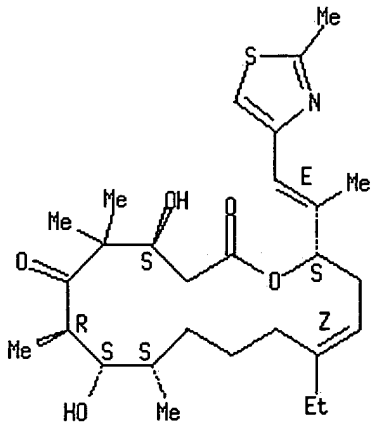
AB A series of 26-substituted epothilones B, e.g. I, were constructed by total synthesis involving a selective Wittig olefination, an aldol reaction and a macrolactonization as key steps.

IT **198475-04-6P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(total synthesis of 26-hydroxyepothilone B and related analogs)

RN 198475-04-6 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 13-ethyl-4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L12 ANSWER 19 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

ACCESSION NUMBER: 1997:724919 HCAPLUS
DOCUMENT NUMBER: 127:346221
TITLE: Synthesis of epothilones A and B in solid and solution phase. [Erratum to document cited in CA127:4950]
AUTHOR(S): Nicolaou, K. C.; Winssinger, N.; Pastor, J.; Ninkovic, S.; Sarabia, F.; He, Y.; Vourloumis, D.; Yang, Z.; Li, T.; Giannakakou, P.; Hamel, E.
CORPORATE SOURCE: Dep. Chemistry, Skaggs Inst. Chem. Biology, Scripps Res. Inst., La Jolla, CA, 92037, USA
SOURCE: Nature (London) (**1997**), 390(6655), 100
CODEN: NATUAS; ISSN: 0028-0836
PUBLISHER: Macmillan Magazines
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Ref. 19, includes, in addn. to a total synthesis of epothilone B, biol.

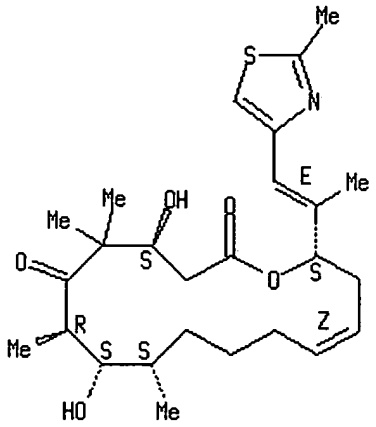
data for compd. 23 and other congeners similar to the reported in the Letter.

IT **186692-73-9P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of a combinatorial library via solid-phase synthesis of epothilone A and soln.-phase synthesis of epothilone B (Erratum))

RN 186692-73-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L12 ANSWER 20 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

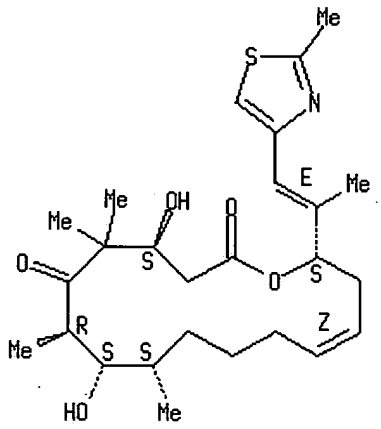
ACCESSION NUMBER: 1997:714315 HCAPLUS
DOCUMENT NUMBER: 128:3560
TITLE: Designed epothilones: combinatorial synthesis, tubulin assembly properties, and cytotoxic action against taxol-resistant tumor cells
AUTHOR(S): Nicolaou, K. C.; Vourloumis, Dionisios; Li, Tianhu; Pastor, Joaquin; Winssinger, Nicolas; He, Yun; Ninkovic, Sacha; Sarabia, Francisco; Vallberg, Hans; Roschangar, Frank; King, N. Paul; Finlay, M. Ray V.; Giannakakou, Pareskevi; Verdier-Pinard, Pascal; Hamel, Ernest
CORPORATE SOURCE: Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, La Jolla, CA, 92037, USA
SOURCE: Angewandte Chemie, International Edition in English (**1997**), 36(19), 2097-2103
CODEN: ACIEAY; ISSN: 0570-0833
PUBLISHER: Wiley-VCH
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The title work demonstrates the power of interfacing combinatorial chem. with chem. biol. as facilitated by solid-phase synthesis, radiofrequency encoded combinatorial chem. and modern biol. assays. A library of 112 epothilones were prepd. by solid-phase synthesis, their structure activity relationships measured by tubulin binding assay and some tested for inhibition of carcinoma cell growth.

IT **186692-73-9P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use);

BIOL (Biological study); PREP (Preparation); USES (Uses)
(combinatorial synthesis of epothilone library, tubulin assembly properties, and cytotoxic action against taxol-resistant tumor cells)
RN 186692-73-9 HCAPLUS
CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.

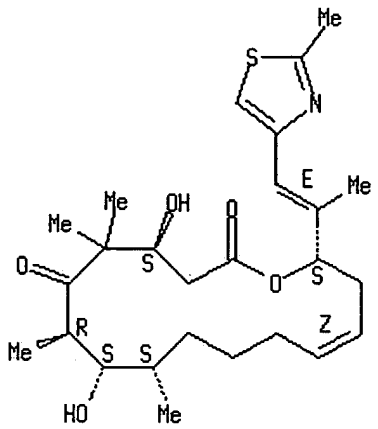


L12 ANSWER 21 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

ACCESSION NUMBER: 1997:714314 HCAPLUS
DOCUMENT NUMBER: 127:358730
TITLE: Structure-activity relationships of the epothilones and the first in vivo comparison with paclitaxel
AUTHOR(S): Su, Dai-Shi; Balog, Aaron; Meng, Dongfang; Bertinato, Peter; Danishefsky, Samuel J.; Zheng, Yu-Huang; Chou, Ting-Chao; He, Lifeng; Horwitz, Susan B.
CORPORATE SOURCE: Laboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, New York, NY, 10021, USA
SOURCE: Angewandte Chemie, International Edition in English (**1997**), 36(19), 2093-2096
CODEN: ACIEAY; ISSN: 0570-0833
PUBLISHER: Wiley-VCH
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The structure-activity relationships of the epothilones and 18 derivs. and analogs were studied. An in vivo comparison of the chemotherapeutic effect of epothilone B with that of paclitaxel was also studied. The chemotherapeutic effect of daily doses of epothilone B (0.7 mg/kg) and paclitaxel (2 mg/kg) in CB-17 SCID mice bearing drug-resistant human CCRF-CEM/VBL xenografts were T/C = 0.33 and T/C = 0.70, resp.
IT **186692-73-9**, Desoxyepothilone A
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(structure-activity relationships of the epothilones and in vivo comparison with paclitaxel)
RN 186692-73-9 HCAPLUS
CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.

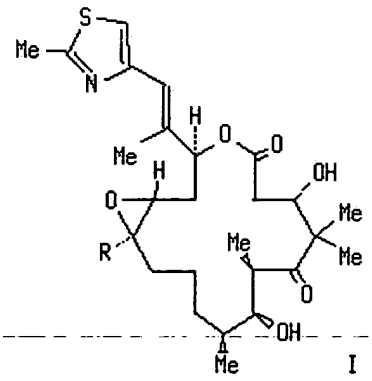


L12 ANSWER 22 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

ACCESSION NUMBER:	1997:665094 HCAPLUS
DOCUMENT NUMBER:	127:293040
TITLE:	Total Syntheses of Epothilones A and B
AUTHOR(S):	Meng, Dongfang; Bertinato, Peter; Balog, Aaron; Su, Dai-Shi; Kamenecka, Ted; Sorensen, Erik; Danishefsky, Samuel J.
CORPORATE SOURCE:	Laboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, New York, NY, 10021, USA
SOURCE:	Journal of the American Chemical Society (**1997**), 119(42), 10073-10092 CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER:	American Chemical Society
DOCUMENT TYPE:	Journal
LANGUAGE:	English
OTHER SOURCE(S):	CASREACT 127:293040

GI



I

AB Convergent, stereocontrolled total syntheses of the microtubule-stabilizing macrolides epothilones A (I; R = H) and B (I; R = Me) have been achieved. Four distinct ring-forming strategies were pursued. Of these four, three were reduced to practice. In one approach, the action of a base on a substance possessing an acetate ester and a nonenolizable aldehyde brought about a remarkably effective macroaldolization simultaneously creating the C2-C3 bond and the hydroxyl-bearing

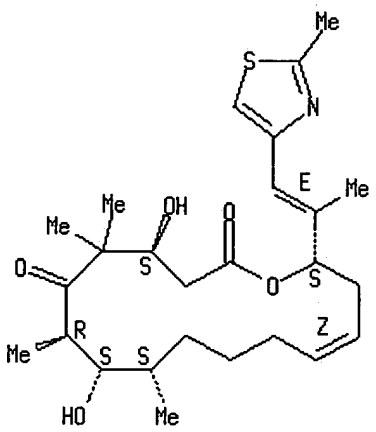
stereocenter at C-3. Alternatively, the 16-membered macrolide of the epothilones could be fashioned through a C12-C13 ring-closing olefin metathesis and through macrolactonization of the appropriate hydroxy acid. The application of a stereospecific B-alkyl Suzuki coupling strategy permitted the establishment of a cis C12-C13 olefin, thus setting the stage for an eventual site- and diastereoselective epoxidn. reaction. The development of a novel cyclopropane solvolysis strategy for incorporating the geminal Me groups of the epothilones, and the use of Lewis acid catalyzed diene-aldehyde cyclocondensation (LACDAC) and asym. allylation methodol. are also noteworthy.

IT **186692-73-9P**, (-)-Desoxyepothilone A
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(syntheses of epothilones A and B via macroaldolization, olefin metathesis and macrolactonization)

RN 186692-73-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L12 ANSWER 23 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

ACCESSION NUMBER: 1997:528753 HCAPLUS
DOCUMENT NUMBER: 127:135660
TITLE: Total Syntheses of Epothilones A and B via a Macrolactonization-Based Strategy
AUTHOR(S): Nicolaou, K. C.; Ninkovic, S.; Sarabia, F.; Vourloumis, D.; He, Y.; Vallberg, H.; Finlay, M. R. V.; Yang, Z.
CORPORATE SOURCE: Department of Chemistry and The Skaggs, Institute for Chemical Biology, La Jolla, CA, 92037, USA
SOURCE: Journal of the American Chemical Society (**1997**), 119(34), 7974-7991
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 127:135660
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

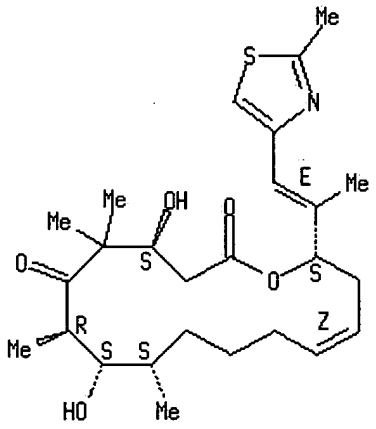
AB The total syntheses of epothilones A (I) (R = H) and B I (R = Me) and several analogs are described. The reported strategy relies on a macrolactonization approach and features selective epoxidn. of the macrocycle double bond in precursors II (R = H, Me) as well as high convergency and flexibility. Building blocks (S)-MeCH2COC(Me)2CH(OSiMe2CMe3)CH2CO2H, (S)-Me3CMe2SiOCH2CH(Me)CH2CH2CH2COR (R = H, Me), (III) [R2 = CH2CH2P+(Ph)3I-; CH2CHO] were constructed by asym. processes and coupled via Wittig, aldol, and macrolactonization reactions to afford the basic skeleton of epothilones and that of several of their analogs by a relatively short route. The utilization of intermediate III [R2 = (E)-CH2CH=C(Me)CH2CH2CH2I], obtained via a stereoselective Wittig reaction and its Enders coupling to SAMP hydrazone, in combination with a stereoselective aldol reaction with the modified substrate (S)-MeCH2COC(Me)2CH(OSiMe2CMe3)CH2CH2OSiMe2CMe3 improved the stereoselectivity and efficiency of the total synthesis of these new and highly potent microtubule binding antitumor agents.

IT **186692-73-9P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(total syntheses of epothilones A and B via a macrolactonization-based strategy)

RN 186692-73-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



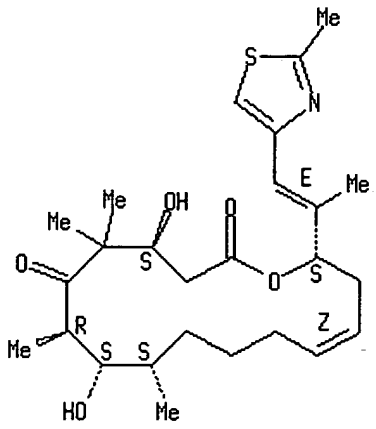
L12 ANSWER 24 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

ACCESSION NUMBER: 1997:528752 HCAPLUS
DOCUMENT NUMBER: 127:149021
TITLE: The Olefin Metathesis Approach to Epothilone A and Its Analogs
AUTHOR(S): Nicolaou, K. C.; He, Y.; Vourloumis, D.; Vallberg, H.; Roschangar, F.; Sarabia, F.; S.Ninkovic; Yang, Z.; Trujillo, J. I.
CORPORATE SOURCE: Department of Chemistry and The Skaggs, Institute for Chemical Biology, La Jolla, CA, 92037, USA
SOURCE: Journal of the American Chemical Society (1997), 119(34), 7960-7973
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

OTHER SOURCE(S): CASREACT 127:149021
GI For diagram(s), see printed CA Issue.
AB The olefin metathesis approach to epothilone A (I) and several diastereomeric analogs is described. Key building blocks II, (S)-OHCCH(Me)CH2CH2CH2CH=CH2, and (S)-MeCH2COC(Me)2CH(OSiMe2CMe3)CH2CO2H were constructed in optically active form and were coupled and elaborated to olefin metathesis precursor III (R = SiMe2CMe3) via an aldol reaction and an esterification coupling. Olefin metathesis of compd. III (R = SiMe2CMe3), under the catalytic influence of RuCl2(:CHPh)(PCy3)2, furnished cis- and trans-cyclic olefins IV (R = SiMe2CMe3). Epoxidn. of (Z)-IV (R = H) gave I and several analogs, whereas epoxidn. of (E)-IV (R = H) resulted in addnl. epothilones. Similar elaboration of isomeric as well as simpler intermediates resulted in yet another series of epothilone analogs and model systems.
IT **186692-73-9P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis of epothilone A and analogs via olefin metathesis)
RN 186692-73-9 HCAPLUS
CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L12 ANSWER 25 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

ACCESSION NUMBER: 1997:456769 HCAPLUS
DOCUMENT NUMBER: 127:50474
TITLE: Preparation of epothilone derivatives as agrochemicals and pharmaceuticals
INVENTOR(S): Hoefle, Gerhard; Kiffe, Michael
PATENT ASSIGNEE(S): Gesellschaft fuer Biotechnologische Forschung Mbh (Gbf), Germany
SOURCE: Ger. Offen., 9 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19542986	A1	19970522	DE 1995-19542986	19951117
WO 9719086	A1	19970529	WO 1996-EP5080	19961118
W: JP, US				

RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

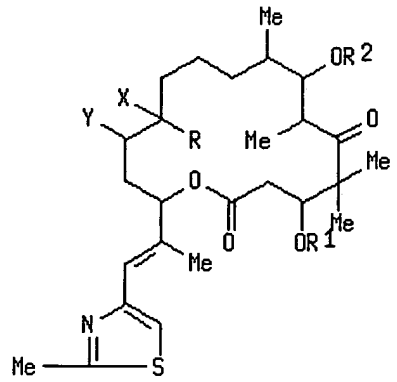
EP 873341	A1	19981028	EP 1996-939097	19961118
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
EP 903348	A1	19990324	EP 1998-121523	19961118
EP 903348	B1	20020605		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2000500757	T2	20000125	JP 1997-519381	19961118
EP 1186606	A1	20020313	EP 2001-127352	19961118
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
AT 218556	E	20020615	AT 1998-121523	19961118
US 6288237	B1	20010911	US 1998-77055	19980803
US 2001034452	A1	20011025	US 2001-836134	20010416

PRIORITY APPLN. INFO.:

DE 1995-19542986	A	19951117
DE 1996-19639456	A	19960925
EP 1996-939097	A3	19961118
WO 1996-EP5080	W	19961118
US 1998-77055	A3	19980803

OTHER SOURCE(S): MARPAT 127:50474

GI



I

AB The title compds., e.g., I [R = H, C1-4 alkyl; R1, R2 = H, C1-6 alkyl, C1-6 acyl, benzoyl, C1-4 trialkylsilyl, benzyl, Ph, C1-6 alkoxy, C6 alkyl-, hydroxy-, and halo-substituted benzyl or phenyl; X, Y = halo, OH, acyloxy, alkoxy, benzoyloxy] , useful as agrochems. and pharmaceuticals (no data), are prepd. Thus, epothilone A in acetone contg. trifluoroacetic acid was heated overnight at 50° and the reaction mixt. was adjusted to pH 7 with 1 M phosphate buffer to give 2 isomers, each in 19% yield.

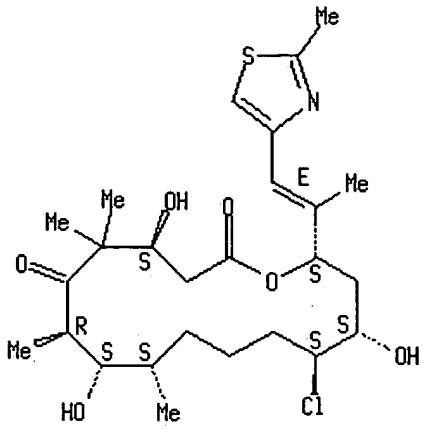
IT **191105-82-5P**

RL: AGR (Agricultural use); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of epothilone derivs. as agrochems. and pharmaceuticals)

RN 191105-82-5 HCAPLUS

CN Oxacyclohexadecane-2,6-dione, 13-chloro-4,8,14-trihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, [4R*,7S*,8R*,9R*,13R*,14R*,16R*(E)]- (9CI) (CA INDEX NAME)

Relative stereochemistry.
Double bond geometry as shown.



L12 ANSWER 26 OF 34 HCAPLUS COPYRIGHT 2002 ACS

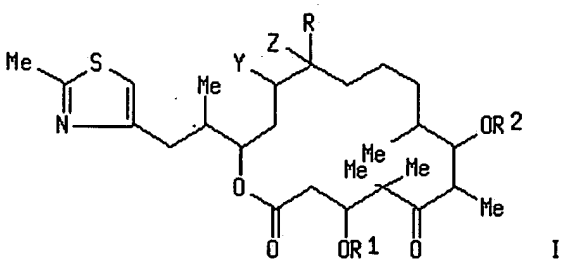
Full Text | Citing References

ACCESSION NUMBER: 1997:443365 HCAPLUS
DOCUMENT NUMBER: 127:81289
TITLE: Preparation of epothilone derivatives as agrochemicals and pharmaceuticals
INVENTOR(S): Hofle, Gerhard; Kiffe, Michael
PATENT ASSIGNEE(S): Gesellschaft Fur Biotechnologische Forschung Mbh (Gbf), Germany; Hofle, Gerhard; Kiffe, Michael
SOURCE: PCT Int. Appl., 38 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9719086	**A1**	**19970529**	**WO 1996-EP5080**	**19961118**
W: JP, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
DE 19542986	**A1**	**19970522**	**DE 1995-19542986**	**19951117**
DE 19639456	**A1**	**19980326**	**DE 1996-19639456**	**19960925**
EP 873341	A1	19981028	EP 1996-939097	19961118
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2000500757	T2	20000125	JP 1997-519381	19961118
US 6288237	B1	20010911	US 1998-77055	19980803

PRIORITY APPLN. INFO.:
DE 1995-19542986 A 19951117
DE 1996-19639456 A 19960925
WO 1996-EP5080 W 19961118

OTHER SOURCE(S): MARPAT 127:81289
GI



I

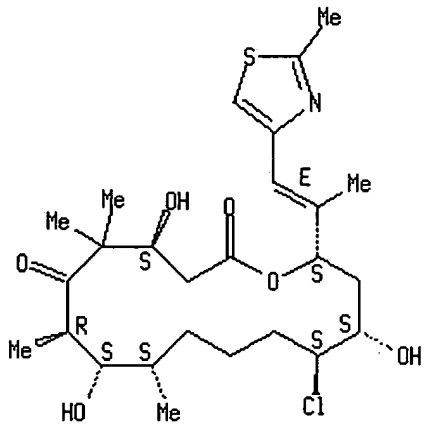
AB The title compds., e.g., I [R = H, C1-4 alkyl; R1, R2 = H, C1-6 alkyl, C1-6 acyl, benzoyl, C1-4 trialkylsilyl, benzyl, Ph, C1-6 alkoxy, C6 alkyl-, hydroxy-, and halo-substituted benzyl or phenyl; X, Y = H, halo, pseudohalo, OH, acyloxy, alkoxy, benzoyloxy; or YZ = O, bond; however, I may not be epothilone A or B] , useful as agrochems. and pharmaceuticals (no data), are prepd. Thus, epothilone A in acetone contg. trifluoroacetic acid was heated overnight at 50° and the reaction mixt. was adjusted to pH 7 with 1 M phosphate buffer to give 2 isomers, each in 19% yield.

IT **191105-82-5P**
RL: AGR (Agricultural use); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of epothilone derivs. as agrochems. and pharmaceuticals)

RN 191105-82-5 HCAPLUS

CN Oxacyclohexadecane-2,6-dione, 13-chloro-4,8,14-trihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, [4R*,7S*,8R*,9R*,13R*,14R*,16R*(E)]- (9CI) (CA INDEX NAME)

Relative stereochemistry.
Double bond geometry as shown.



L12 ANSWER 27 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

ACCESSION NUMBER: 1997:430309 HCAPLUS
DOCUMENT NUMBER: 127:108793
TITLE: Stereoselective syntheses and evaluation of compounds in the 8-desmethylepothilone A series: some surprising observations regarding their chemical and biological properties
AUTHOR(S): Balog, Aaron; Betinato, Peter; Su, Dai-Shi; Meng, Dongfang; Sorensen, Erik; Danishefsky, Samuel J.; Zheng, Yu-Huang; Chou, Ting-Chao; He, Lifeng; Horwitz, Susan B.
CORPORATE SOURCE: Lab. Bioorganic Chem., Sloan-Kettering Inst. Cancer Res., New York, NY, 10021, USA
SOURCE: Tetrahedron Letters (1997), 38(26), 4529-4532
CODEN: TELEAY; ISSN: 0040-4039
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 127:108793

AB The title compds. have been synthesized in a convergent way by recourse to a Weiler type dianion construction.

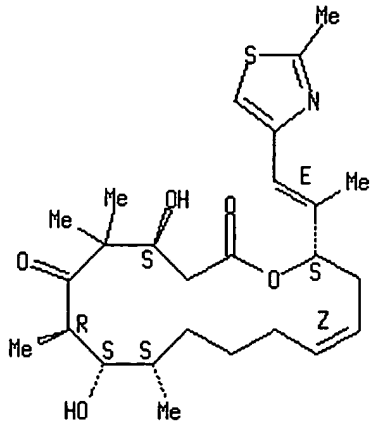
IT **186692-73-9**, Desoxyepothilone A
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); BIOL (Biological study)
(stereoselective syntheses and evaluation of compds. in the 8-desmethylepothilone A series)

RN 186692-73-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

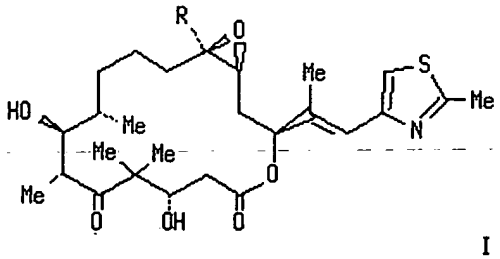
Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L12 ANSWER 28 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

ACCESSION NUMBER: 1997:330310 HCAPLUS
DOCUMENT NUMBER: 127:4950
TITLE: Synthesis of epothilones A and B in solid and solution phase
AUTHOR(S): Nicolaou, K. C.; Winssinger, N.; Pastor, J.; Ninkovic, S.; Sarabia, F.; He, Y.; Vourloumis, D.; Yang, Z.; Li, T.; Giannakakou, P.; Hamel, E.
CORPORATE SOURCE: Dep. Chemistry, Skaggs Inst. Chem. Biology, Scripps Res. Inst., La Jolla, CA, 92037, USA
SOURCE: Nature (London) (**1997**), 387(6630), 268-272
CODEN: NATUAS; ISSN: 0028-0836
PUBLISHER: Macmillan Magazines
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 127:4950
GI



I

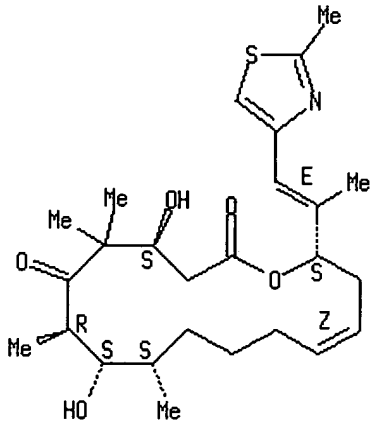
AB Epothilones A (I; R = H) and B (I: R = Me), two compds. that were recently isolated from myxobacterium Sorangium cellulosum strain 90, have generated intense interest among chemists, biologists and clinicians owing to the structural complexity, unusual mechanism of interaction with microtubules and anticancer potential of these mols. Like taxol, they exhibit

cytotoxicity against tumor cells by inducing microtubule assembly and stabilization, even in taxol-resistant cell lines. Following the structural elucidation of these mols. by X-ray crystallog. in 1996, several synthesis of epothilones A and B have been reported, indicative of the potential importance of these mols. in the cancer field. Here we report the first solid-phase synthesis of epothilone A, the total synthesis of epothilone B, and the generation of a small epothilone library. The solid-phase synthesis applied here to epothilone A could open up new possibilities in natural-product synthesis and, together with soln.-phase synthesis of other epothilones, paves the way for the generation of large combinatorial libraries of these important mols. for biol. screening.

IT **186692-73-9P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of a combinatorial library via solid-phase synthesis of epothilone A and soln.-phase synthesis of epothilone B)

RN 186692-73-9 HCAPLUS
CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L12 ANSWER 29 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

ACCESSION NUMBER: 1997:302059 HCAPLUS
DOCUMENT NUMBER: 127:4948
TITLE: Total synthesis of (-)-epothilone B: an extension of the Suzuki coupling method and insights into structure-activity relationships of the epothilones
AUTHOR(S): Su, Dai-Shi; Meng, Dongfang; Bertinato, Peter; Balog, Aaron; Sorensen, Erik J.; Danishefsky, Samuel J.; Zheng, Yu-Huang; Chou, Ting-Chao; He, Lifeng; Horwitz, Susan B.
CORPORATE SOURCE: Laboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, New York, NY, 10021, USA
SOURCE: Angewandte Chemie, International Edition in English (**1997**), 36(7), 757-759
CODEN: ACIEAY; ISSN: 0570-0833
PUBLISHER: VCH
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 127:4948

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

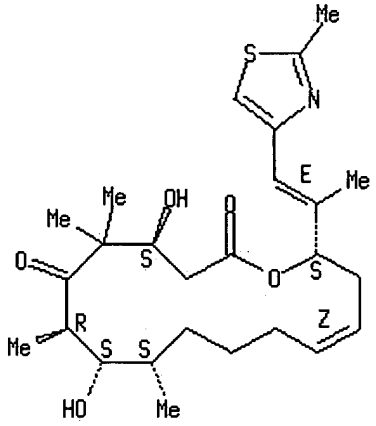
AB (-)-Epothilone B (I; R = Me, X = O) and desoxyepothilone B (I; R = Me, X = bond) were prepd. via Suzuki coupling of (Z)-vinyl iodide II with borane III. I (R = H, Me, X = O, bond) and the E-isomers of I (R = H, Me, X = bond) were tested for efficacy against drug-sensitive and resistant CCRF-CEM cell lines (IC50 = 0.0004 - 0.262 μM).

IT **186692-73-9**, Desoxyepothilone A
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(synthesis of epothilone B via a Suzuki coupling and insights into antitumor structure-activity relationships)

RN 186692-73-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

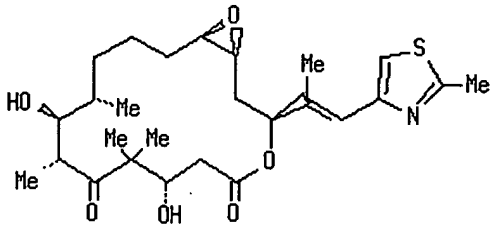
Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



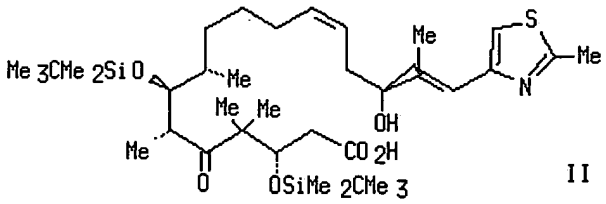
L12 ANSWER 30 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

ACCESSION NUMBER: 1997:206419 HCAPLUS
DOCUMENT NUMBER: 126:251010
TITLE: Total synthesis of epothilone A: the macrolactonization approach
AUTHOR(S): Nicolaou, K. C.; Sarabia, Francisco; Ninkovic, Sacha; Yang, Zhen
CORPORATE SOURCE: Dep. Chem., Skaggs Inst. Chem. Biol. Scripps Res. Inst., La Jolla, CA, 92037, USA
SOURCE: Angewandte Chemie, International Edition in English (1997), 36(5), 525-527
CODEN: ACIEAY; ISSN: 0570-0833
PUBLISHER: VCH
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 126:251010
GI



I



II

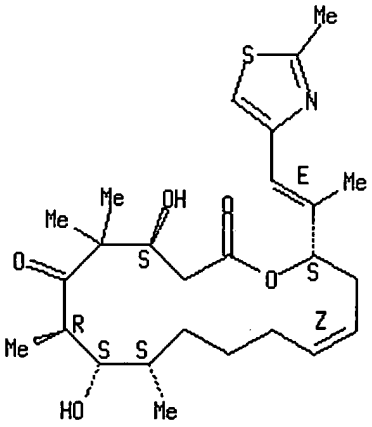
AB Epothilone A (I) was prepd. via a highly convergent and flexible route with macrolactonization of hydroxy acid II as the key step.

IT **186692-73-9P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(total synthesis of epothilone A via a macrolactonization approach)

RN 186692-73-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.

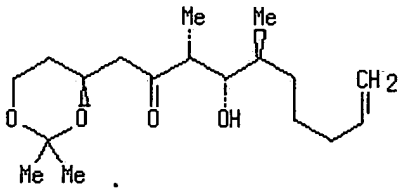


L12 ANSWER 31 OF 34 HCAPLUS COPYRIGHT 2002 ACS

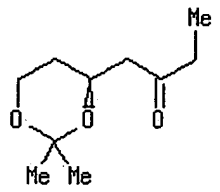
Full Text | Citing References

ACCESSION NUMBER:	1997:206418 HCAPLUS
DOCUMENT NUMBER:	126:277316
TITLE:	Total synthesis of (-)-epothilone A
AUTHOR(S):	Schinzer, Dieter; Limberg, Anja; Bauer, Armin; Boehm, Oliver M.; Cordes, Martin
CORPORATE SOURCE:	Dip. Chim., Inst. Org. Chem. Tech. Univ. Hagenring, Braunschweig, D-38106, Germany
SOURCE:	Angewandte Chemie, International Edition in English (1997), 36(5), 523-524

CODEN: ACIEAY; ISSN: 0570-0833
PUBLISHER: VCH
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 126:277316
GI



I



II

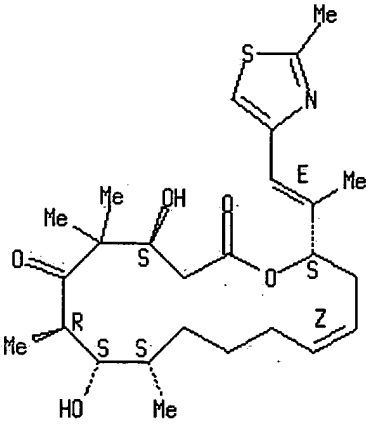
AB Stereoselective total synthesis of (-)-epothilone A and epothilone C was reported. The key step was the diastereoselective prepn. of intermediate ketone I by an aldol condensation of II with (S)-2-methyl-6-heptenal.

IT **186692-73-9P**, Epothilone C
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(total synthesis of (-)-epothilone A)

RN 186692-73-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L12 ANSWER 32 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

ACCESSION NUMBER: 1997:175662 HCAPLUS
DOCUMENT NUMBER: 126:225133
TITLE: Remote Effects in Macrolide Formation through Ring-Forming Olefin Metathesis: An Application to the Synthesis of Fully Active Epothilone Congeners

AUTHOR(S): Meng, Dongfang; Su, Dai-Shi; Balog, Aaron; Bertinato, Peter; Sorensen, Erik J.; Danishefsky, Samuel J.; Zheng, Yu-Huang; Chou, Ting-Chao; He, Lifeng; Horwitz, Susan B.
CORPORATE SOURCE: Laboratories for Bioorganic Chemistry and Biochemical Pharmacology, Sloan-Kettering Institute for Cancer Research, New York, NY, 10021, USA

SOURCE: Journal of the American Chemical Society (1997),

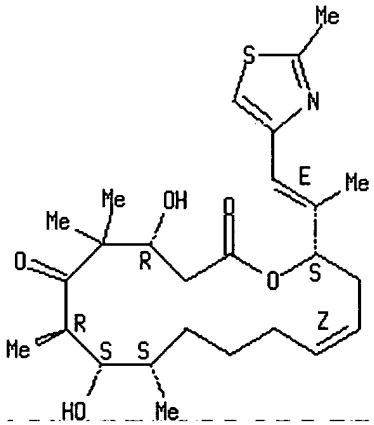
119(11), 2733-2734
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 126:225133
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB A ring closing olefin metathesis strategy for the synthesis of the previously encountered desoxyepothilone A (I) is described. A merging of the alkyl segment II (carbons 12-21) and acyl segment III (carbons 3-11) through an intermol. aldol-condensation reaction provided substrates needed for ring closing olefin metathesis. Thus, thiazole IV underwent olefin metathesis in C6H6 contg. 50 mol % (PhCH:)[P(cyclohexyl)3]2RuCl2 to give 65% II and its E-isomer (Z:E 1:2). The results of these cyclization indicate a remarkable sensitivity to permutations of functionality at centers remote from the site of olefin metathesis. The in vitro biol. activity of E and Z desoxyepothilone as well as several related congeners is also described. I has IC50 range of 0.012-0.022 μM against drug-sensitive and -resistant human leukemic CCRF-CEM cell lines.

IT **188259-95-2P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of antitumor epothilone congeners via ring-forming olefin metathesis)
RN 188259-95-2 HCAPLUS
CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4R,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.

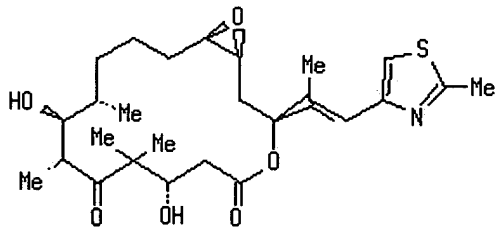


L12 ANSWER 33 OF 34 HCAPLUS COPYRIGHT 2002 ACS

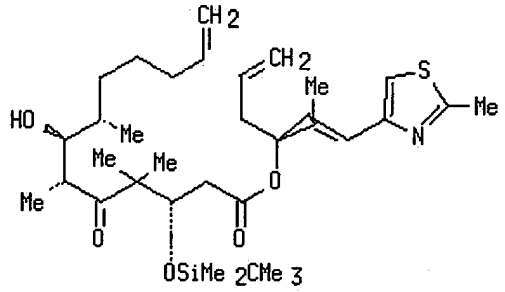
Full Text | Citing References

ACCESSION NUMBER: 1997:117381 HCAPLUS
DOCUMENT NUMBER: 126:199371
TITLE: Total synthesis of epothilone A: the olefin metathesis approach
AUTHOR(S): Yang, Zhen; He, Yun; Vourloumis, Dionisios; Vallberg,

Hans; Nicolaou, K. C.
CORPORATE SOURCE: Department Chemistry Skaggs Institute Chemical Biology, Scripps Research Institute, La Jolla, CA, 92037, USA
SOURCE: Angewandte Chemie, International Edition in English (**1997**), 36(1/2), 166-168
CODEN: ACIEAY; ISSN: 0570-0833
PUBLISHER: VCH
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 126:199371
GI



I



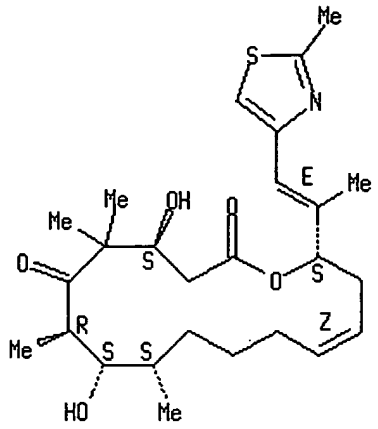
II

AB The asym. total synthesis of epothilone A (I) from EtCOCMe2CHO, (S)-H2C:CH(CH2)3CHMeCHO and Et 2-methylthiazole-4-carboxylate via metathesis of olefin II is described.

IT **186692-73-9P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(total synthesis of epothilone A via an olefin metathesis)

RN 186692-73-9 HCAPLUS
CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

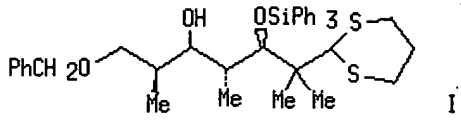
Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



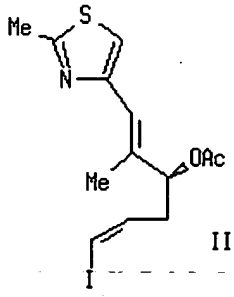
L12 ANSWER 34 OF 34 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

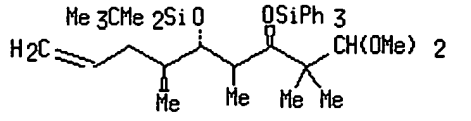
ACCESSION NUMBER: 1997:72321 HCAPLUS
DOCUMENT NUMBER: 126:144023
TITLE: Total synthesis of (-)-epothilone A
AUTHOR(S): Balog, Aaron; Meng, Dongfang; Kamenecka, Ted; Bertinato, Peter; Su, Dai-Shi; Sorensen, Erik J.; Danishefsky, Samuel J.
CORPORATE SOURCE: Lab. for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, New York, NY, 10021, USA
SOURCE: Angewandte Chemie, International Edition in English (**1997**), Volume Date 1996, 35(23/24), 2801-2803
CODEN: ACIEAY; ISSN: 0570-0833
PUBLISHER: VCH
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I



II



III

AB (-)-Epothilone A was prepd. from dithiane I, (R)-glycidol and [(2-methyl-1,3-thiazol-4-yl)methyl]diphenylphosphine oxide via a B-alkyl Suzuki coupling of thiazole II with acetal III followed by closure of the macrocycle with an aldol reaction.

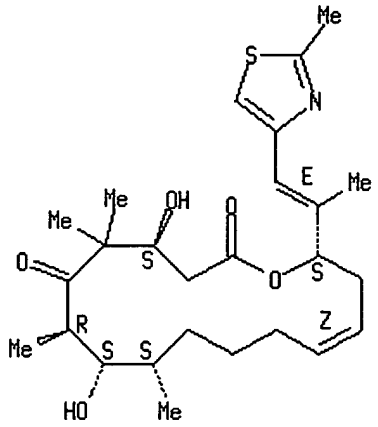
IT **186692-73-9P**

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(total synthesis of (-)-epothilone A via a B-alkyl Suzuki coupling

followed by closure of the macrocycle with an aldol reaction)
RN 186692-73-9 HCAPLUS
CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



=> **file caold**

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	186.26	474.49

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-24.78	-24.78

FILE 'CAOLD' ENTERED AT 17:10:28 ON 22 AUG 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907-1966
FILE LAST UPDATED: 01 May 1997 (19970501/UP)

This file contains CAS Registry Numbers for easy and accurate substance identification. Title keywords, authors, patent assignees, and patent information, e.g., patent numbers, are now searchable from 1907-1966. TIFF images of CA abstracts printed between 1907-1966 are available in the PAGE display formats.

This file supports REGistRY for direct browsing and searching of all substance data from the REGISTRY file. Enter HELP FIRST for more information.

=> **d his**

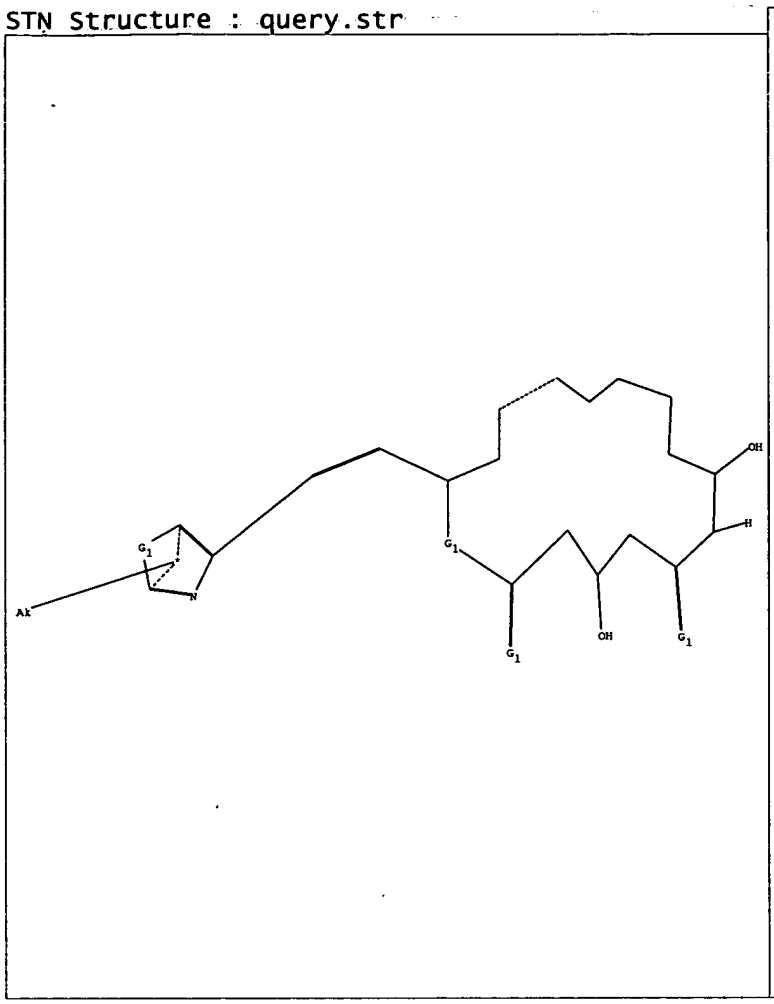
(FILE 'HOME' ENTERED AT 16:57:10 ON 22 AUG 2002)

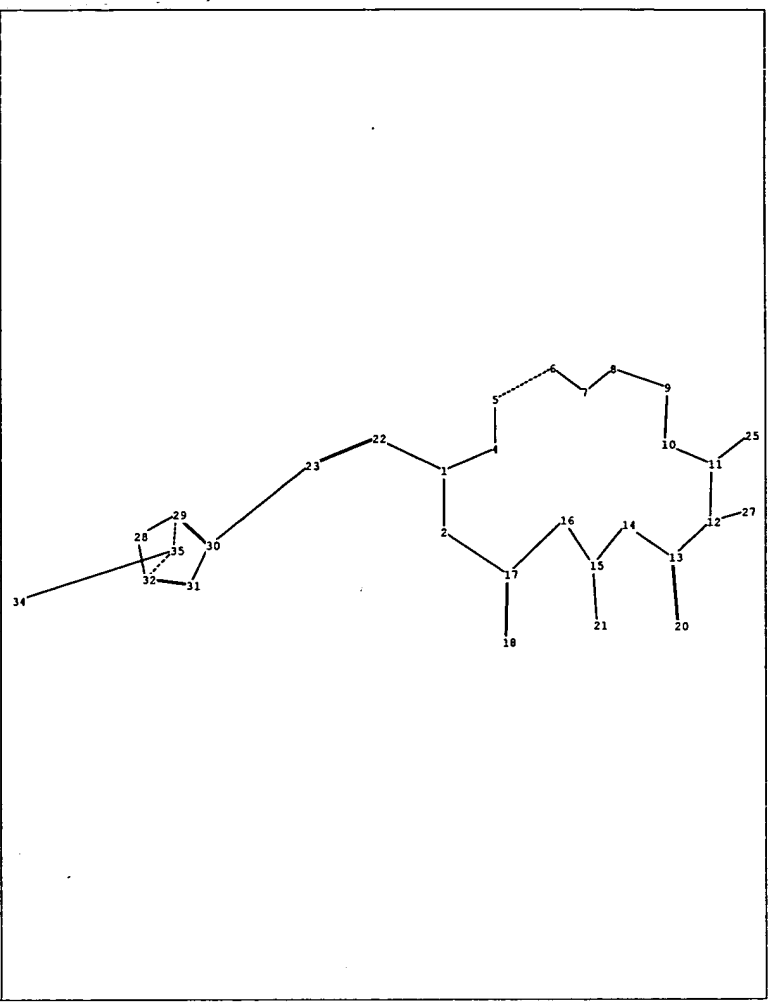
FILE 'REGISTRY' ENTERED AT 16:57:18 ON 22 AUG 2002
L1 STRUCTURE UPLOADED
L2 11 S L1
L3 235 S L1 FULL

FILE 'HCAPLUS' ENTERED AT 17:02:57 ON 22 AUG 2002

```
L4          134 S L3

     FILE 'REGISTRY' ENTERED AT 17:03:04 ON 22 AUG 2002
L5               STRUCTURE UPLOADED
L6            8 S L5
L7          121 S L5 FULL

     FILE 'HCAPLUS' ENTERED AT 17:07:15 ON 22 AUG 2002
L8          132 S L7
L9           34 S L8 AND PD < SEPTEMBER 1998
L10           6 S L8 AND KLAR, U?/AU
L11           0 S L9 AND KLAR, U?/AU
L12          34 S L9 NOT L10

     FILE 'CAOLD' ENTERED AT 17:10:28 ON 22 AUG 2002

=> s l7
L13           0 L7

=> log y
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.38     474.87

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                       ENTRY    SESSION
CA SUBSCRIBER PRICE                                     0.00     -24.78

STN INTERNATIONAL LOGOFF AT 17:10:52 ON 22 AUG 2002
```

STN Structure : query.str





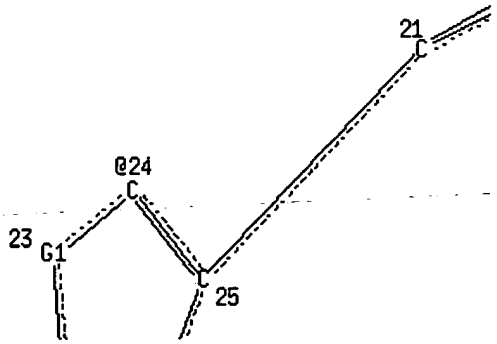
chain nodes :
18 20 21 22 23 25 27 34
ring nodes :
1 2 4 5 6 7 8 9 10 11 12 13 14 15 16 17 28 29 30 31 32
chain bonds :
1-22 11-25 12-27 13-20 15-21 17-18 22-23 23-30
ring bonds :
1-2 1-4 2-17 4-5 5-6 6-7 7-8 8-9 9-10 10-11 11-12 12-13 13-14 14-15 15-16
16-17 28-29 28-32 29-30 30-31 31-32
exact/norm bonds :
1-2 1-4 1-22 2-17 4-5 5-6 6-7 7-8 8-9 9-10 10-11 11-12 11-25 12-13 12-27
13-14 13-20 14-15 15-16 15-21 16-17 17-18 22-23 23-30 28-29 28-32 29-30 30-31
31-32
isolated ring systems :
containing 1 : 28 :

G1:O,S

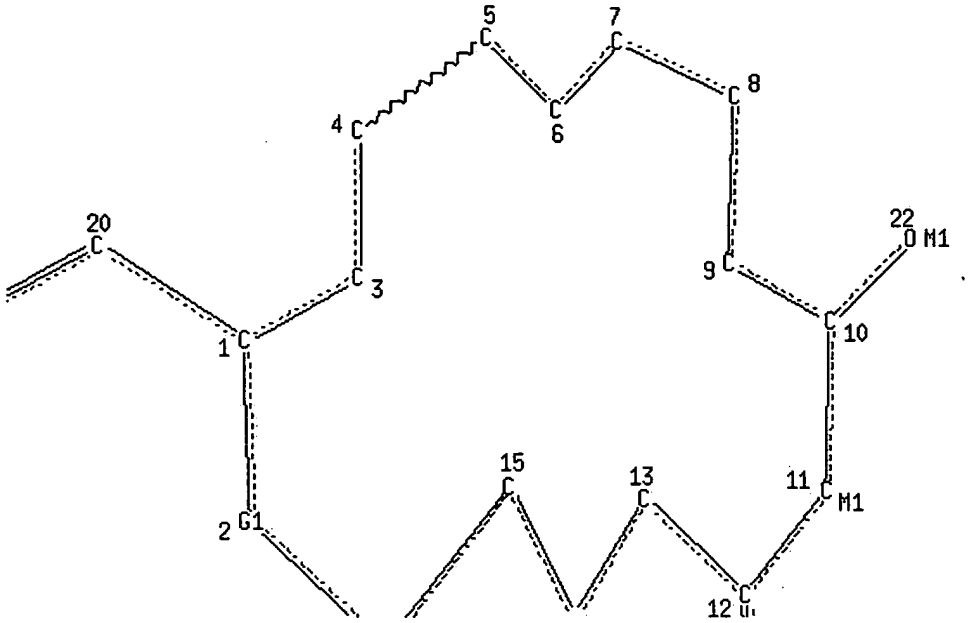
G2:CH3,Et

Match level :
1:Atom 2:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom 11:Atom 12:Atom
13:Atom 14:Atom 15:Atom 16:Atom 17:Atom 18:Atom 20:Atom 21:CLASS 22:CLASS
23:CLASS 25:CLASS 27:CLASS 28:Atom 29:Atom 30:Atom 31:Atom 32:Atom 34:CLASS
35:CLASS

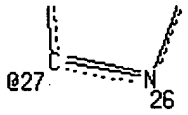
```
=> file reg
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                        ENTRY    SESSION
FULL ESTIMATED COST                                      1.90       2.11

FILE 'REGISTRY' ENTERED AT 18:16:22 ON 22 AUG 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2002 American Chemical Society (ACS)

STRUCTURE FILE UPDATES:   21 AUG 2002  HIGHEST RN 444646-89-3
DICTIONARY FILE UPDATES:  21 AUG 2002  HIGHEST RN 444646-89-3

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Calculated physical property data is now available.  See HELP PROPERTIES
for more information.  See STNote 27, Searching Properties in the CAS
Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=>
L2      STRUCTURE UPLOADED

=> d l2
L2 HAS NO ANSWERS
L2              STR
 0 29 S 30
```



Page 1-A

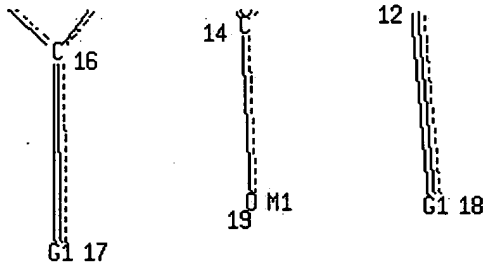


Page 1-B



Ak @28

Page 2-A



Page 2-B
VAR G1=29/30
VPA 28-24/27 S
NODE ATTRIBUTES:

HCOUNT	IS M1	AT	11
HCOUNT	IS M1	AT	19
HCOUNT	IS M1	AT	22
NSPEC	IS R	AT	1
NSPEC	IS R	AT	2
NSPEC	IS R	AT	3
NSPEC	IS R	AT	4
NSPEC	IS R	AT	5
NSPEC	IS R	AT	6
NSPEC	IS R	AT	7
NSPEC	IS R	AT	8
NSPEC	IS R	AT	9
NSPEC	IS R	AT	10
NSPEC	IS R	AT	11
NSPEC	IS R	AT	12
NSPEC	IS R	AT	13
NSPEC	IS R	AT	14
NSPEC	IS R	AT	15
NSPEC	IS R	AT	16
NSPEC	IS C	AT	17

```
NSPEC   IS C      AT  18
NSPEC   IS C      AT  19
NSPEC   IS C      AT  20
NSPEC   IS C      AT  21
NSPEC   IS C      AT  22
NSPEC   IS R      AT  23
NSPEC   IS R      AT  24
NSPEC   IS R      AT  25
NSPEC   IS R      AT  26
NSPEC   IS R      AT  27
NSPEC   IS C      AT  28
DEFAULT MLEVEL IS ATOM
MLEVEL  IS CLASS  AT  19 20 21 22 28
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC I
NUMBER OF NODES IS  30

STEREO ATTRIBUTES: NONE


=> s l2
SAMPLE SEARCH INITIATED 18:17:01 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -     76 TO ITERATE

100.0% PROCESSED      76 ITERATIONS                              18 ANSWERS
SEARCH TIME: 00.00.02

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:          997 TO     2043
PROJECTED ANSWERS:             106 TO      614

L3           18 SEA SSS SAM L2

=> s l2 full
THE ESTIMATED SEARCH COST FOR FILE 'REGISTRY' IS 139.90 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N or END:y
FULL SEARCH INITIATED 18:17:10 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -   1426 TO ITERATE

100.0% PROCESSED    1426 ITERATIONS                            292 ANSWERS
SEARCH TIME: 00.00.03

L4          292 SEA SSS FUL L2

=> file hcaplus
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                               140.66     142.77

FILE 'HCAPLUS' ENTERED AT 18:17:16 ON 22 AUG 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2002 AMERICAN CHEMICAL SOCIETY (ACS)
```

FILE COVERS 1907 - 22 Aug 2002 VOL 137 ISS 8
FILE LAST UPDATED: 21 Aug 2002 (20020821/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

CAS roles have been modified effective December 16, 2001. Please check your SDI profiles to see if they need to be revised. For information on CAS roles, enter HELP ROLES at an arrow prompt or use the CAS Roles thesaurus (/RL field) in this file.

=> **s l4**
L5 143 L4

=> s l5 and pd < september 1998
18872712 PD < SEPTEMBER 1998
(PD<19980900)
L6 35 L5 AND PD < SEPTEMBER 1998

=> **d l6, ibib abs fhitstr, 1**

L6 ANSWER 1 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

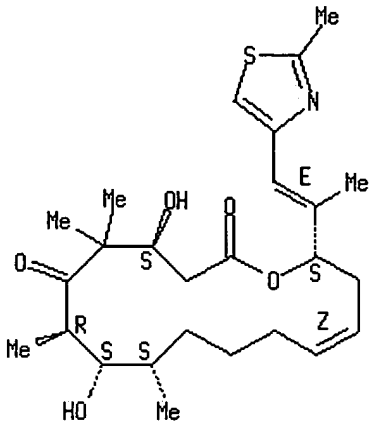
ACCESSION NUMBER: 2000:316343 HCAPLUS
Correction of: 1997:528752
DOCUMENT NUMBER: 132:293587
Correction of: 127:149021
TITLE: The Olefin Metathesis Approach to Epothilone A and Its Analogs
AUTHOR(S): Nicolaou, K. C.; He, Y.; Vourloumis, D.; Vallberg, H.; Roschangar, F.; Sarabia, F.; Ninkovic, S.; Yang, Z.; Trujillo, J. I.
CORPORATE SOURCE: Institute for Chemical Biology, La Jolla, CA, 92037, USA
SOURCE: Journal of the American Chemical Society (**1997**), 119(34), 7960-7973
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The olefin metathesis approach to epothilone A (I) and several diastereomeric analogs is described. Key building blocks II, (S)-OHCCH(Me)CH2CH2CH2CH=CH2, and (S)-MeCH2COC(Me)2CH(OSiMe2CMe3)CH2CO2H were constructed in optically active form and were coupled and elaborated to olefin metathesis precursor III (R = SiMe2CMe3) via an aldol reaction and an esterification coupling. Olefin metathesis of compd. III (R = SiMe2CMe3), under the catalytic influence of RuCl2(:CHPh)(PCy3)2, furnished cis- and trans-cyclic olefins IV (R = SiMe2CMe3). Epoxidn. of (Z)-IV (R = H) gave I and several analogs, whereas epoxidn. of (E)-IV (R = H) resulted in addnl. epothilones. Similar elaboration of isomeric as well as simpler intermediates resulted in yet another series of epothilone analogs and model systems.
IT **186692-73-9P**

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis of epothilone A and analogs via olefin metathesis)
RN 186692-73-9 HCAPLUS
CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



=> **d his**

(FILE 'HOME' ENTERED AT 18:12:21 ON 22 AUG 2002)

FILE 'REGISTRY' ENTERED AT 18:12:27 ON 22 AUG 2002
L1 STRUCTURE UPLOADED

FILE 'REGISTRY' ENTERED AT 18:16:22 ON 22 AUG 2002
L2 STRUCTURE UPLOADED
L3 18 S L2
L4 292 S L2 FULL

FILE 'HCAPLUS' ENTERED AT 18:17:16 ON 22 AUG 2002
L5 143 S L4
L6 35 S L5 AND PD < SEPTEMBER 1998

=> **d l6, ibib abs fhitstr, 1-35**

L6 ANSWER 1 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

ACCESSION NUMBER: 2000:316343 HCAPLUS
Correction of: 1997:528752
DOCUMENT NUMBER: 132:293587
Correction of: 127:149021
TITLE: The Olefin Metathesis Approach to Epothilone A and Its Analogs
AUTHOR(S): Nicolaou, K. C.; He, Y.; Vourloumis, D.; Vallberg, H.; Roschangar, F.; Sarabia, F.; Ninkovic, S.; Yang, Z.; Trujillo, J. I.
CORPORATE SOURCE: Institute for Chemical Biology, La Jolla, CA, 92037, USA
SOURCE: Journal of the American Chemical Society (**1997**), 119(34), 7960-7973
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal
LANGUAGE: English
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

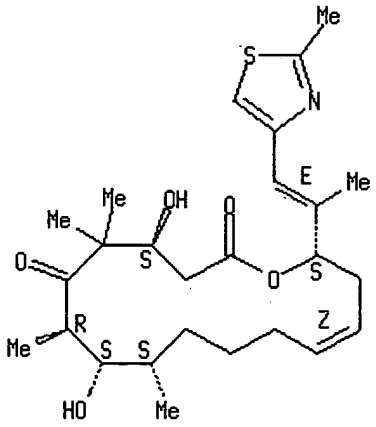
AB The olefin metathesis approach to epothilone A (I) and several diastereomeric analogs is described. Key building blocks II, (S)-OHCCH(Me)CH2CH2CH2CH=CH2, and (S)-MeCH2COC(Me)2CH(OSiMe2CMe3)CH2CO2H were constructed in optically active form and were coupled and elaborated to olefin metathesis precursor III (R = SiMe2CMe3) via an aldol reaction and an esterification coupling. Olefin metathesis of compd. III (R = SiMe2CMe3), under the catalytic influence of RuCl2(:CHPh)(PCy3)2, furnished cis- and trans-cyclic olefins IV (R = SiMe2CMe3). Epoxidn. of (Z)-IV (R = H) gave I and several analogs, whereas epoxidn. of (E)-IV (R = H) resulted in addnl. epothilones. Similar elaboration of isomeric as well as simpler intermediates resulted in yet another series of epothilone analogs and model systems.

IT **186692-73-9P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis of epothilone A and analogs via olefin metathesis)

RN 186692-73-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L6 ANSWER 2 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

ACCESSION NUMBER: 1999:19340 HCAPLUS
DOCUMENT NUMBER: 130:217758
TITLE: Desoxyepothilone B is curative against human tumor xenografts that are refractory to paclitaxel
AUTHOR(S): Chou, Ting-Chao; Zhang, Xiu-Guo; Harris, Christina R.; Kuduk, Scott D.; Balog, Aaron; Savin, Kenneth A.; Bertino, Joseph R.; Danishefsky, Samuel J.
CORPORATE SOURCE: Molecular Pharmacology and Therapeutics Program, Sloan-Kettering Institute for Cancer Research, New York, NY, 10021, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (**1998**), 95(26), 15798-15802

CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

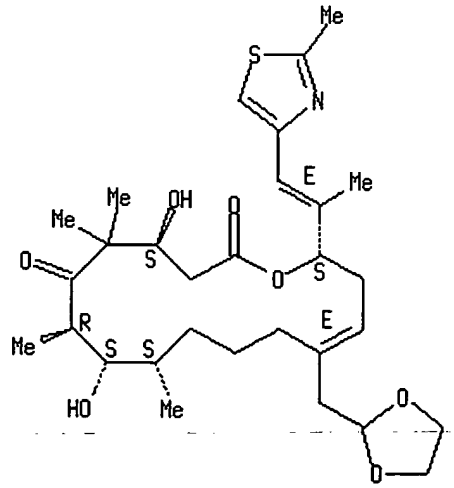
AB The epothilones are naturally occurring, cytotoxic macrolides that function through a paclitaxel (Taxol)-like mechanism. Although structurally dissimilar, both classes of mols. lead to the arrest of cell division and eventual cell death by stabilizing cellular microtubule assemblies. The epothilones differ in their ability to retain activity against multidrug-resistant (MDR) cell lines and tumors where paclitaxel fails. In the current account, we focus on the relationship between epothilone and paclitaxel in the context of tumors with multiple drug resistance. The epothilone analog Z-12,13-desoxyepothilone B (dEpoB) is >35,000-fold more potent than paclitaxel in inhibiting cell growth in the MDR DC-3F/ADX cell line. Various formulations, routes, and schedules of i.v. administration of dEpoB have been tested in nude mice. Slow infusion with a Cremophor-ethanol vehicle proved to be the most beneficial in increasing efficacy and decreasing toxicity. Although dEpoB performed similarly to paclitaxel in sensitive tumors xenografts (MX-1 human mammary and HT-29 colon tumor), its effects were clearly superior against MDR tumors. When dEpoB was administered to nude mice bearing our MDR human lymphoblastic T cell leukemia (CCRF-CEM/paclitaxel), dEpoB demonstrated a full curative effect. For human mammary adenocarcinoma MCF-7/Adr cells refractory to paclitaxel, dEpoB reduced the established tumors, markedly suppressed tumor growth, and surpassed other commonly used chemotherapy drugs such as adriamycin, vinblastine, and etoposide in beneficial effects.

IT **198475-07-9**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(antitumor activity of desoxyepothilone B analogs)

RN 198475-07-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 13-(1,3-dioxolan-2-ylmethyl)-4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13E,16S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



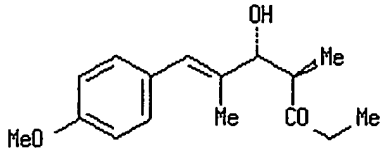
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 3 OF 35 HCAPLUS COPYRIGHT 2002 ACS

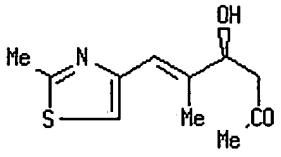
Full Text | Citing References

ACCESSION NUMBER: 1998:805542 HCAPLUS

DOCUMENT NUMBER: 130:153488
TITLE: The antibody catalysis route to the total synthesis of epothilones
AUTHOR(S): Sinha, Subhash C.; Barbas, Carlos F., III; Lerner, Richard A.
CORPORATE SOURCE: The Skaggs Institute for Chemical Biology and the Department of Molecular Biology, The Scripps Research Institute, La Jolla, CA, 92037, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (**1998**), 95(25), 14603-14608
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 130:153488
GI



I

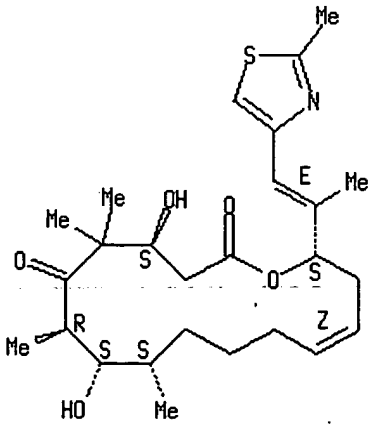


II

AB A total synthesis of epothilones A and C via antibody-catalyzed aldol and retro-aldol reactions was described. Epothilone precursors (+)-I and (-)-II were prepd. using aldolase antibody 38C2 as a catalyst. These precursors were then converted to epothilones A and C to complete the total synthesis.

IT **186692-73-9P**, Epothilone C
RL: BPN (Biosynthetic preparation); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(total synthesis of epothilones via antibody 38C2 catalyzed retro-aldol reactions)
RN 186692-73-9 HCAPLUS
CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



REFERENCE COUNT: 62 THERE ARE 62 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 4 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

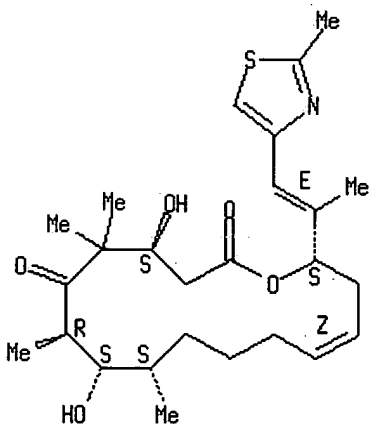
ACCESSION NUMBER: 1998:760826 HCAPLUS
DOCUMENT NUMBER: 130:95407
TITLE: Derivatization of the C12-C13 functional groups of epothilones A, B and C
AUTHOR(S): Sefkow, Michael; Kiffe, Michael; Hofle, Gerhard
CORPORATE SOURCE: Gesellschaft fur Biotechnologische Forschung mbH, Abt. Naturstoffchemie, Braunschweig, D-38124, Germany
SOURCE: Bioorganic & Medicinal Chemistry Letters (**1998**), 8(21), 3031-3036
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 130:95407

AB Epothilone A reacted with hydrohalic acids to give C12-C13 halohydrin regioisomers (ratios: 2:1 - 4:1), whereas epothilone B gave under the same conditions the isomerically pure C12 halo C13 hydroxy deriv. With non-nucleophilic Bronstedt acids and with Lewis acids a highly solvent dependent product distribution and some unexpected rearrangement products were obsd. Epothilone C bearing a double bond between C12 and C13 was regioselectively dihydroxylated or hydrogenated at that position.

IT **186692-73-9**, Epothilone C
RL: RCT (Reactant); RACT (Reactant or reagent)
(derivatization of the C12-C13 functional groups of epothilones A, B and C)

RN 186692-73-9 HCAPLUS
CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 5 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

ACCESSION NUMBER: 1998:732784 HCAPLUS
DOCUMENT NUMBER: 130:81320
TITLE: Easy access to the epothilone family - synthesis of epothilone B
AUTHOR(S): Mulzer, Johann; Mantoulidis, Andreas; Ohler, Elisabeth
CORPORATE SOURCE: Inst. fur Organische Chemie, Univ. Wien, Vienna, A-1090, Austria

SOURCE: Tetrahedron Letters (**1998**), 39(47), 8633-8636
CODEN: TELEAY; ISSN: 0040-4039
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 130:81320

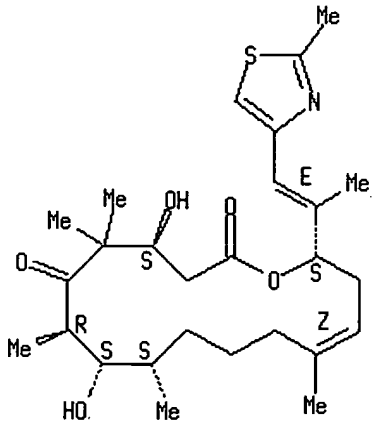
AB An easy access to four out of five naturally occurring epothilones (A-E) is reported. Key steps are an enantioselective Mukaiyama type aldol reaction, (E)- and (Z)-selective olefinations, and a sulfone alkylation.

IT **189453-10-9P**, Epothilone D
RL: SPN (Synthetic preparation); PREP (Preparation)
(synthesis of epothilone B)

RN 189453-10-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.

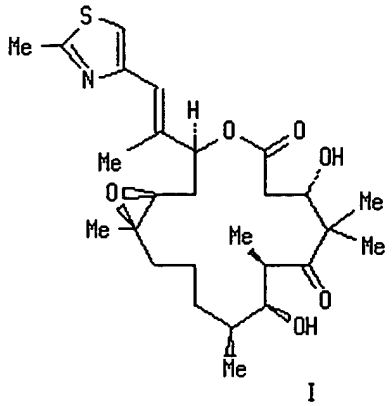


REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

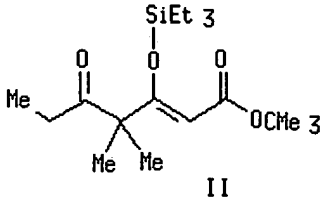
L6 ANSWER 6 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

ACCESSION NUMBER: 1998:726876 HCAPLUS
DOCUMENT NUMBER: 130:81319
TITLE: A novel aldol condensation with 2-methyl-4-pentenal and its application to an improved total synthesis of epothilone B
AUTHOR(S): Balog, Aaron; Harris, Christina; Savin, Kenneth; Zhang, Xiu-Guo; Chou, Ting Chao; Danishefsky, Samuel J.
CORPORATE SOURCE: Laboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, New York, NY, 10021, USA
SOURCE: Angewandte Chemie, International Edition (**1998**), 37(19), 2675-2678
CODEN: ACIEF5; ISSN: 1433-7851
PUBLISHER: Wiley-VCH Verlag GmbH
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 130:81319
GI



I



II

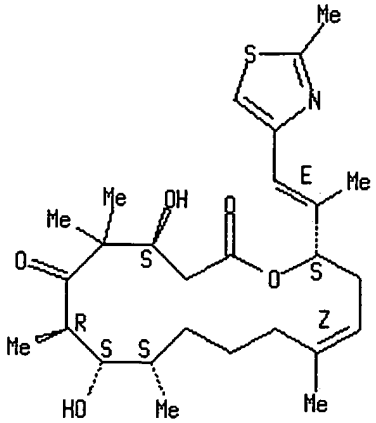
AB Epothilone B was prepd. in 9 steps via aldol condensation of (S)-2-methyl-4-pentenal with the enolate I.

IT **189453-10-9P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(novel aldol condensation with 2-methyl-4-pentenal and application to improved total synthesis of epothilone B)

RN 189453-10-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 7 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

ACCESSION NUMBER: 1998:534644 HCAPLUS
DOCUMENT NUMBER: 129:239597
TITLE: Desoxyepothilone B: an efficacious microtubule-targeted antitumor agent with a promising in vivo profile relative to epothilone B
AUTHOR(S): Chou, Ting-Chao; Zhang, Xiu-Guo; Balog, Aaron; Su, Dai-Shi; Meng, Dongfang; Savin, Kenneth; Bertino, Joseph R.; Danishefsky, Samuel J.
CORPORATE SOURCE: Molecular Pharmacology and Therapeutics Program, Cornell University Graduate School of Medical Sciences, New York, NY, 10021, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (**1998**), 95(16), 9642-9647

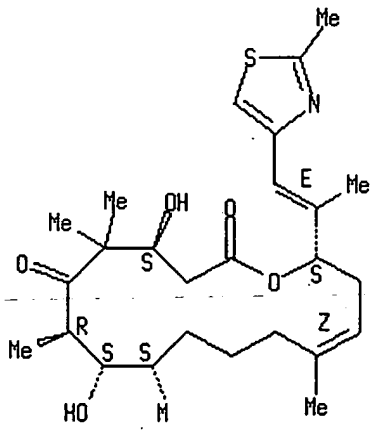
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A new class of 16-membered macrolides, the epothilones (Epos), has been synthesized and evaluated for antitumor potential in vitro and in vivo. Recent studies in these and other labs. showed that epothilones and paclitaxel (paclitaxel) share similar mechanisms of action in stabilizing microtubule arrays as indicated by binding-displacement studies, substitution for paclitaxel in paclitaxel-dependent cell growth, and electron microscopic examns. The present study examd. cell growth-inhibitory effects in two rodent and three human tumor cell lines and their drug-resistant sublines. Although paclitaxel showed as much as 1,970-fold cross-resistance to the sublines resistant to paclitaxel, adriamycin, vinblastine, or actinomycin D, most epothilones exhibit little or no cross-resistance. In multidrug-resistant CCRF-CEM/VBL100 cells, IC50 values for EpoA (1), EpoB (2), desoxyEpoA (3) (dEpoA), desoxyEpoB (4) (dEpoB), and paclitaxel were 0.02, 0.002, 0.012, 0.017, and 4.14 μM, resp. In vivo studies, using i.p. administration, indicated that the parent, EpoB, was highly toxic to mice and showed little therapeutic effect when compared with a lead compd., dEpoB. More significantly, dEpoB (25-40 mg/kg, Q2Dx5, i.p.) showed far superior therapeutic effects and lower toxicity than paclitaxel, doxorubicin, camptothecin, or vinblastine (at maximal tolerated doses) in parallel expts. For mammary adenocarcinoma xenografts resistant to adriamycin, MCF-7/Adr, superior therapeutic effects were obtained with dEpoB compared with paclitaxel when i.p. regimens were used. For ovarian adenocarcinoma xenografts, SK-OV-3, dEpoB (i.p.), and paclitaxel (i.v.) gave similar therapeutic effects. In nude mice bearing a human mammary carcinoma xenograft (MX-1), marked tumor regression and cures were obtained with dEpoB.

IT **189453-10-9**, Desoxyepothilone B
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(desoxyepothilone B is an efficacious microtubule-targeted antitumor agent with a promising in vivo profile relative to epothilone B)

RN 189453-10-9 HCAPLUS
CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L6 ANSWER 8 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

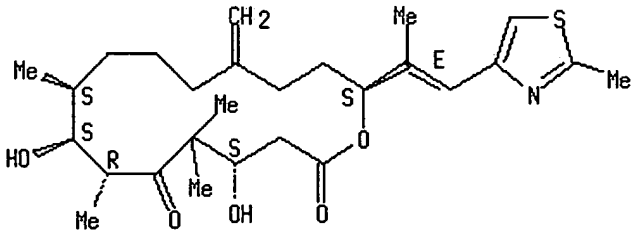
ACCESSION NUMBER: 1998:503765 HCAPLUS
DOCUMENT NUMBER: 129:244965
TITLE: Synthesis and biological properties of C12,13-cyclopropyl-epothilone A and related epothilones
AUTHOR(S): Nicolaou, K. C.; Finlay, M. Ray V.; Ninkovic, Sacha; King, N. Paul; He, Yun; Li, Tianhu; Sarabia, Francisco; Vourloumis, Dionisios
CORPORATE SOURCE: Dep. Chemistry, The Skaggs Inst. Chem. Biol., The Scripps Res. Inst., La Jolla, CA, 92037, USA
SOURCE: Chemistry & Biology (**1998**), 5(7), 365-372
CODEN: CBOLE2; ISSN: 1074-5521
PUBLISHER: Current Biology Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 129:244965

AB Background: The epothilones are natural substances that are potently cytotoxic, having an almost identical mode of action to Taxol as tubulin-polymn. and microtubule-stabilizing agents. The development of detailed structure-activity relationships for these compds. and the further elucidation of their mechanism of action is of high priority. Results: The chem. synthesis of the C12,13-cyclopropyl analog of epothilone A and its C12,13-trans-diastereoisomer has been accomplished. These compds. and several other epothilone analogs have been screened for their ability to induce tubulin polymn. and death of a no. of tumor cells. Several interesting structure-activity trends within this family of compds. were identified. Conclusions: The results of the biol. tests conducted in this study have demonstrated that, although a no. of positions on the epothilone skeleton are amenable to modification without significant loss of biol. activity, the replacement of the epoxide moiety of epothilone A with a cyclopropyl group leads to total loss of activity.

IT **213312-66-4**
RL: RCT (Reactant); RACT (Reactant or reagent)
(synthesis and biol. properties of C12,13-cyclopropyl-epothilone A and related epothilones)

RN 213312-66-4 HCAPLUS
CN Oxacyclohexadecane-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-13-methylene-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,16S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.

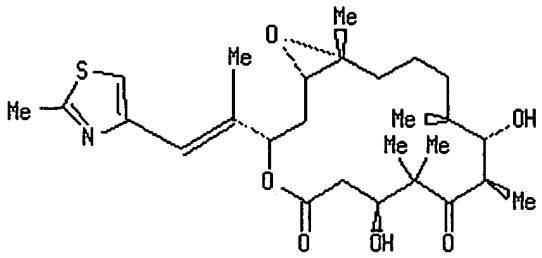


L6 ANSWER 9 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

ACCESSION NUMBER: 1998:492150 HCAPLUS
DOCUMENT NUMBER: 129:216449
TITLE: Total synthesis of (-)-epothilone B
AUTHOR(S): May, Scott A.; Grieco, Paul A.
CORPORATE SOURCE: Department of Chemistry and Biochemistry, Montana State University, Bozeman, MT, 59717, USA
SOURCE: Chemical Communications (Cambridge) (**1998**), (15), 1597-1598

CODEN: CHCOFS; ISSN: 1359-7345
PUBLISHER: Royal Society of Chemistry
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

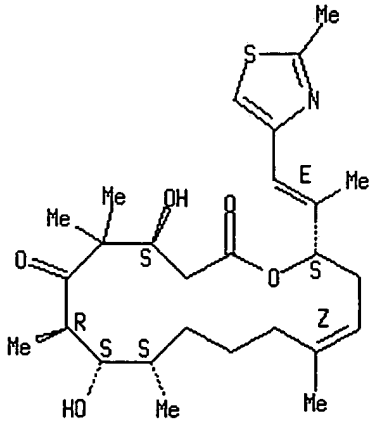
AB The sixteen-membered ring macrolide (-)-epothilone B (I) has been synthesized by a route which features stereospecific methylation of an (E)-γ,δ-epoxy acrylate, the use of a double asym. reaction employing (R,R)-diisopropyltartrate and (E)-crotylboronate, ring closure by means of an olefin metathesis reaction.

IT **189453-10-9P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(total synthesis of (-)-epothilone B)

RN 189453-10-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L6 ANSWER 10 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

ACCESSION NUMBER: 1998:405952 HCAPLUS
DOCUMENT NUMBER: 129:81625
TITLE: Preparation of epothilone analogs as anticancer agents
INVENTOR(S): Nicolaou, Costa Kyriacos; He, Yun; Ninkovic, Sacha; Pastor, Joaquin; Roschangar, Frank; Sarabia, Francisco; Vallberg, Hans; Vourloumis, Dionisios; Winssinger, Nicolas; Yang, Zhen; King, Nigel Paul; et al.
PATENT ASSIGNEE(S): Novartis A.-G., Switz.; Scripps Research Institute
SOURCE: PCT Int. Appl., 213 pp.

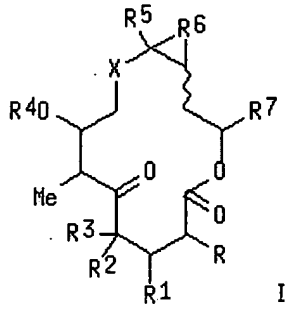
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9825929	**A1**	**19980618**	**WO 1997-EP7011**	**19971212**
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9857577	**A1**	**19980703**	**AU 1998-57577**	**19971212**
AU 746597	B2	20020502		
EP 944634	A1	19990929	EP 1997-953808	19971212
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 9714140	A	20000229	BR 1997-14140	19971212
CN 1246862	A	20000308	CN 1997-181771	19971212
JP 2001504856	T2	20010410	JP 1998-526247	19971212

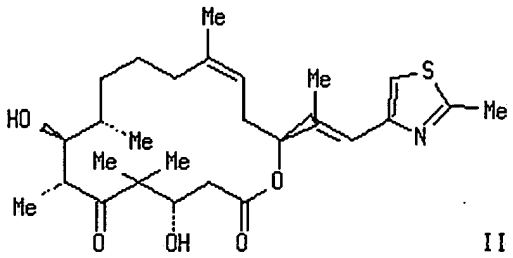
PRIORITY APPLN. INFO.:

US 1996-32864P	P	19961213
US 1997-856533	A	19970514
US 1997-923869	A2	19970904
WO 1997-EP7011	W	19971212

OTHER SOURCE(S): MARPAT 129:81625
GI



I



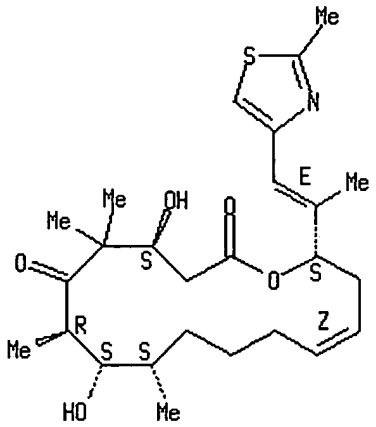
II

AB Epothilone A, epothilone B, analogs of epothilone and libraries of epothilone analogs of formula I [X = (CH2)n; n = 1-5; R1 = OH, OMe, absent; R2, R3 = H, CH2, Me; R4 = H, Me, protecting group; R5 = H, Me, CHO, (substituted) CO2H, etc.; R6 = O, CH2, absent; R7 = thiazolealkyl, etc.] are synthesized. Epothilone A and B are known anticancer agents that derive their anticancer activity by the prevention of mitosis through the induction and stabilization of microtubulin assembly. Several of the analogs are demonstrated to have a superior cytotoxic activity as compared to epothilone A or epothilone B as demonstrated by their enhanced ability to induce the polymn. and stabilization of microtubules. Thus, II was prepd. and was shown to induce tubulin polymn. at 94% relative to GTP, and inhibit carcinoma cell growth.

IT **186692-73-9P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of epothilone analogs as anticancer agents)
RN 186692-73-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

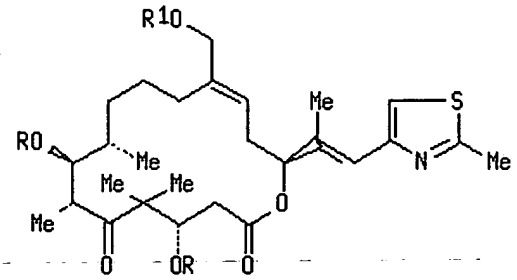
Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L6 ANSWER 11 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

ACCESSION NUMBER: 1998:378435 HCAPLUS
DOCUMENT NUMBER: 129:189151
TITLE: Total synthesis of 26-hydroxy-epothilone B and related analogs via a macrolactonization based strategy
AUTHOR(S): Nicolaou, K. C.; Finlay, M. Ray V.; Ninkovic, Sacha; Sarabia, Francisco
CORPORATE SOURCE: Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, La Jolla, CA, 92037, USA
SOURCE: Tetrahedron (**1998**), 54(25), 7127-7166
CODEN: TETRAB; ISSN: 0040-4020
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 129:189151
GI



I

AB The chem. synthesis of a series of 26-substituted epothilones B was described. Fully protected 26-hydroxydesoxy-epothilone B I (R = SiMe2CMe3, R1 = CPh3), prepd. via a macrolactonization strategy, served as a common precursor to the designed epothilones described. The synthesized compds. were members of a large epothilone library of a no. of antitumor agents.

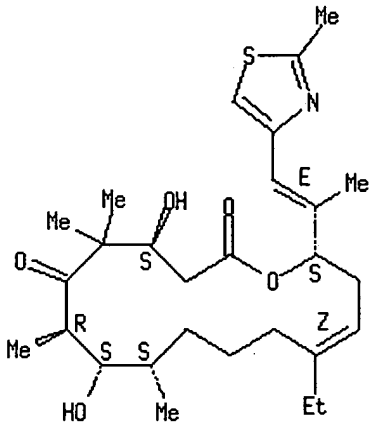
IT **198475-04-6P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT

(Reactant or reagent)
(total synthesis of 26-hydroxy-epothilone B and related analogs via a macrolactonization based strategy)

RN 198475-04-6 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 13-ethyl-4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L6 ANSWER 12 OF 35 HCAPLUS COPYRIGHT 2002 ACS

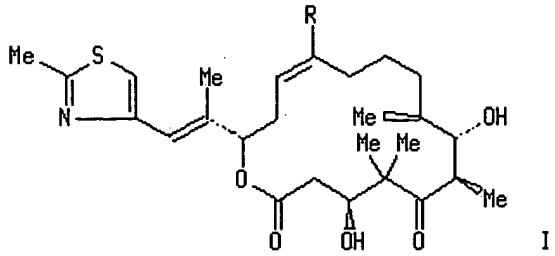
Full Text | Citing References

ACCESSION NUMBER: 1998:352834 HCAPLUS
DOCUMENT NUMBER: 129:53436
TITLE: Epothilone C, D, E and F, production process, and their use as cytostatics well as phytosanitary agents
INVENTOR(S): Reichenbach, Hans; Hofle, Gerhard; Gerth, Klaus; Steinmetz, Heinrich
PATENT ASSIGNEE(S): Gesellschaft Fur Biotechnologische Forschung m.b.H. (GBF), Germany; Reichenbach, Hans; Hofle, Gerhard; Gerth, Klaus; Steinmetz, Heinrich
SOURCE: PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

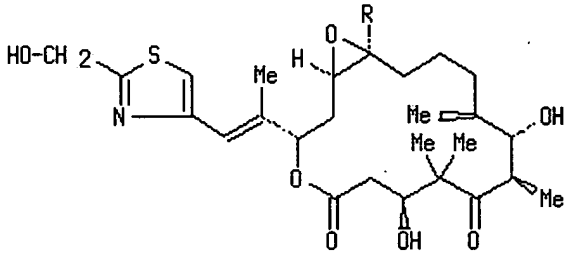
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9822461	**A1**	**19980528**	**WO 1997-EP6442**	**19971118**
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9854837	**A1**	**19980610**	**AU 1998-54837**	**19971118**
ZA 9710384	A	19990518	ZA 1997-10384	19971118
EP 941227	A1	19990915	EP 1997-951233	19971118
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
CN 1237970	A	19991208	CN 1997-199814	19971118
BR 9713363	A	20000125	BR 1997-13363	19971118

JP 2001504474	T2	20010403	JP 1998-523208		19971118
TW 408119	B	20001011	TW 1997-86117334		19980121
NO 9902338	A	19990514	NO 1999-2338		19990514
KR 2000053308	A	20000825	KR 1999-704302		19990514
PRIORITY APPLN. INFO.:			DE 1996-19647580	A	19961118
			DE 1997-19707506	A	19970225
			WO 1997-EP6442	W	19971118

GI



I



II

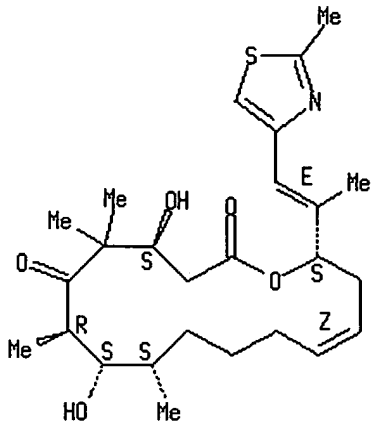
AB The present invention concerns the epothilones, esp. epothilone C [I; R = H] and epothilone D [I; R = Me] as well as epothilone E [II; R = H] and epothilone F [II; R = Me], the prodn. process, and their application for producing therapeutic agents, including cytostatic agents as well as phytosanitary agents.

IT **186692-73-9P**, Epothilone C
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(epothilone C, D, E and F, prodn. process, and use as cytostatics well as phytosanitary agents)

RN 186692-73-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L6 ANSWER 13 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

ACCESSION NUMBER: 1998:163596 HCAPLUS
DOCUMENT NUMBER: 128:217229
TITLE: Method for producing epothilones and the intermediate products obtained during the production process
INVENTOR(S): Schinzer, Dieter; Limberg, Anja; Bohm, Oliver M.; Bauer, Armin; Cordes, Martin
PATENT ASSIGNEE(S): Novartis Aktiengesellschaft, Switz.; Schinzer, Dieter; Limberg, Anja; Bohm, Oliver M.; Bauer, Armin; Cordes, Martin
SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9808849	**A1**	**19980305**	**WO 1997-DE111**	**19970115**
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
DE 19636343	**C1**	**19971023**	**DE 1996-19636343**	**19960830**
DE 19645361	**A1**	**19980430**	**DE 1996-19645361**	**19961028**
DE 19645362	**A1**	**19980430**	**DE 1996-19645362**	**19961028**
AU 9721493	**A1**	**19980319**	**AU 1997-21493**	**19970115**
AU 716610	B2	20000302		
EP 923583	A1	19990623	EP 1997-914077	19970115
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2001500851	T2	20010123	JP 1998-511141	19970115

PRIORITY APPLN. INFO.:
DE 1996-19636343 A 19960830
DE 1996-19645361 A 19961028
DE 1996-19645362 A 19961028
WO 1997-DE111 W 19970115

OTHER SOURCE(S): CASREACT 128:217229; MARPAT 128:217229
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

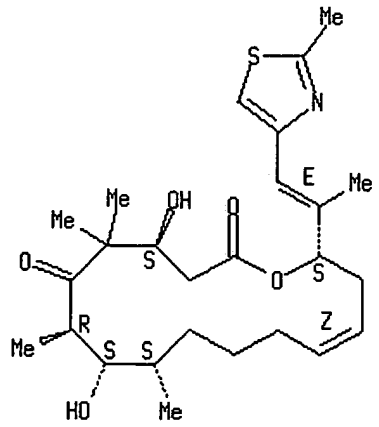
AB A method for producing epothilones I [R = H (A), Me (B)] is characterized by reaction of thiazole II with carboxylic acid III (B = CH2Ph, THP, silyl protecting group; R = H, Me), followed by olefin metathesis in the presence of a noble metal catalyst, hydroxyl deprotection and epoxidn. Thus, epothilone A (I; R = H) was prepd. via acylation of II with III (R = H, B = SiMe2CMe3) in CH2Cl2 contg. DCC and DMAP, followed by olefin metathesis in CH2Cl2 contg. catalytic benzylidenebis(tricyclohexylphosphine)ruthenium dichloride, desilylation with aq. HF in Et2O/MeCN and epoxidn. with dimethyldioxirane in acetone. Epothilones A and B are natural substances which are produced by microorganisms and have similar properties to those of taxol and, therefore, are of interest to the pharmaceutical chem.

IT **186692-73-9P**, Epothilone C
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of epothilones via olefin metathesis)

RN 186692-73-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

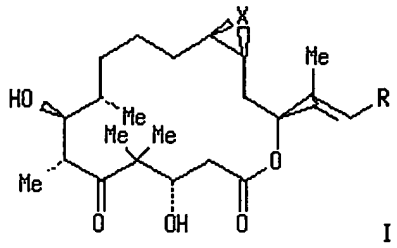
Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L6 ANSWER 14 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

ACCESSION NUMBER: 1998:150476 HCAPLUS
DOCUMENT NUMBER: 128:230166
TITLE: Total synthesis of epothilone E and analogs with modified side chains through the Stille coupling reaction
AUTHOR(S): Nicolaou, K. C.; He, Yun; Roschangar, Frank; King, N. Paul; Vourloumis, Dionisios; Li, Tianhu
CORPORATE SOURCE: Department of Chemistry, Skaggs Inst. for Chemical Biology, Scripps Res. Inst., La Jolla, CA, 92037, USA
SOURCE: Angewandte Chemie, International Edition (**1998**), 37(1/2), 84-87
CODEN: ACIEF5; ISSN: 1433-7851
PUBLISHER: Wiley-VCH Verlag GmbH
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 128:230166
GI



I

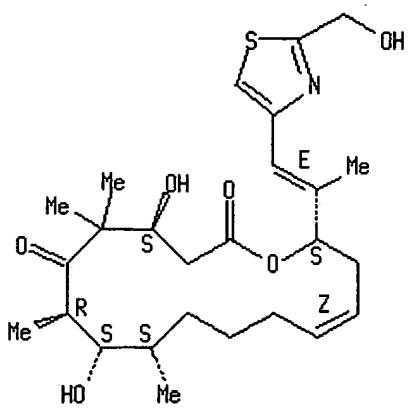
AB The first total synthesis of epothilone E [I; R = 2-(hydroxymethyl)thiazol-4-yl, X = O] in which an olefin metathesis is used to form the macrocyclic lactone and a Stille coupling reaction is used to form the side chain is reported. The Stille coupling reaction was used to prep. deoxygenated side-chain analogs I [R = thiazol-4-yl, thiazol-5-yl, thiazol-2-yl, 2-(5-acetoxypentyl)thiazol-4-yl, 2-piperidinothiazol-4-yl, 2-(methylthio)thiazol-4-yl, 2-furyl, 2-thienyl, Ph, 3-pyridyl; X = bond].

IT **204513-12-2P**, Desoxyepothilone E
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(total synthesis of epothilone E and analogs through the Stille coupling reaction)

RN 204513-12-2 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-16-[(1E)-2-[2-(hydroxymethyl)-4-thiazolyl]-1-methylethenyl]-5,5,7,9-tetramethyl-, (4S,7R,8S,9S,13Z,16S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L6 ANSWER 15 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

ACCESSION NUMBER: 1998:121923 HCAPLUS
DOCUMENT NUMBER: 128:252599
TITLE: Farnesyl transferase inhibitors cause enhanced mitotic sensitivity to taxol and epothilones
AUTHOR(S): Moasser, Mark M.; Sepp-Lorenzino, Laura; Kohl, Nancy E.; Oliff, Allen; Balog, Aaron; Su, Dai-Shi; Danishefsky, Samuel J.; Rosen, Neal
CORPORATE SOURCE: Department of Medicine, Memorial Sloan-Kettering Cancer Center, Sloan-Kettering Institute, New York, NY, 10021, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (**1998**), 95(4), 1369-1374
CODEN: PNASA6; ISSN: 0027-8424

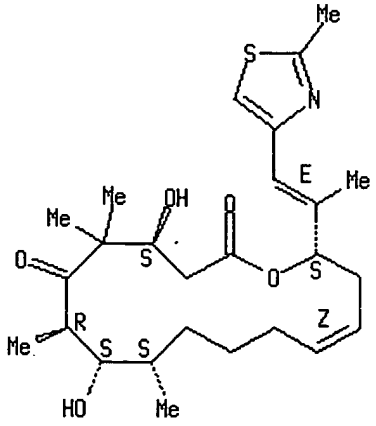
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB An important class of cellular proteins, which includes members of the p21ras family, undergoes post-translational farnesylation, a modification required for their partition to membranes. Specific farnesyl transferase inhibitors (FTIs) have been developed that selectively inhibit the processing of these proteins. FTIs have been shown to be potent inhibitors of tumor cell growth in cell culture and in murine models and at doses that cause little toxicity to the animal. These data suggest that these drugs might be useful therapeutic agents. We now report that, when FTI is combined with some cytotoxic antineoplastic drugs, the effects on tumor cells are additive. No interference is noted. Furthermore, FTI and agents that prevent microtubule depolymn., such as taxol or epothilones, act synergistically to inhibit cell growth. FTI causes increased sensitivity to induction of metaphase block by these agents, suggesting that a farnesylated protein may regulate the mitotic check point. The findings imply that FTI may be a useful agent for the treatment of tumors with wild-type ras that are sensitive to taxanes.

IT **186692-73-9**, Desoxyepothilone A
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(farnesyl transferase inhibitors cause enhanced mitotic sensitivity to taxol and epothilones)

RN 186692-73-9 HCAPLUS
CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.

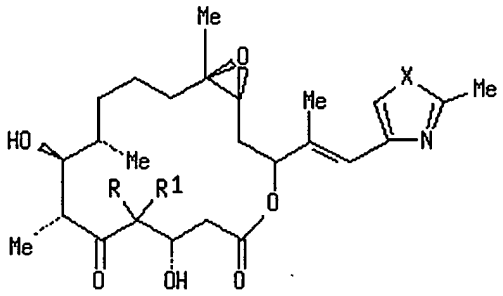


L6 ANSWER 16 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

ACCESSION NUMBER: 1998:50907 HCAPLUS
DOCUMENT NUMBER: 128:180246
TITLE: Total synthesis of oxazole- and cyclopropane-containing epothilone B analogs by the macrolactonization approach
AUTHOR(S): Nicolaou, K. C.; Sarabia, Francisco; Finlay, M. Ray V.; Ninkovic, Sacha; King, N. Paul; Vourloumis, Dionisios; He, Yun
CORPORATE SOURCE: Department of Chemistry and The Skaggs Institute for Chemical Biology The Scripps Research Institute, La Jolla, CA, 92037, USA
SOURCE: Chemistry--A European Journal (**1997**), 3(12), 1971-1986

CODEN: CEUJED; ISSN: 0947-6539
PUBLISHER: Wiley-VCH Verlag GmbH
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



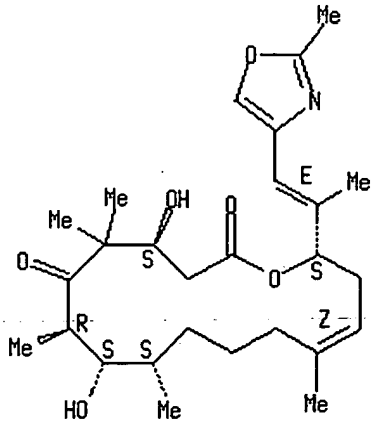
I

AB In order to probe structure-activity relationships in the epothilone area, two series of epothilone B analogs were designed and synthesized. The first series contg. an oxazole moiety in place of a thiazole on the side chain was constructed via utilization of key intermediates whereas the second series contg. an ethano group instead of the gem-di-Me group at position 4 was synthesized. A Yamaguchi-type macrolactonization reaction was used to construct the macrocycle from a secoacid, which was assembled, in both cases, via a) an aldol reaction, b) an Enders alkylation, and c) a Wittig-type reaction. This convergent strategy provided access to oxazole and 4,4-ethano analogs, e.g., I (R = R1 = Me, X = O, S; RR1 = CH2CH2, X = O, S).

IT **198571-09-4P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(total synthesis of oxazole- and cyclopropane-contg. epothilone B analogs via macrolactonization)

RN 198571-09-4 HCAPLUS
CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-[(1E)-1-methyl-2-(2-methyl-4-oxazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L6 ANSWER 17 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

ACCESSION NUMBER: 1998:50906 HCAPLUS
DOCUMENT NUMBER: 128:140541

TITLE: Total synthesis of oxazole- and cyclopropane-containing epothilone A analogs by the olefin metathesis approach

AUTHOR(S): Nicolaou, K. C.; Vallberg, Hans; King, N. Paul; Roschangar, Frank; He, Yun; Vourloumis, Dionisios; Nicolaou, Christopher G.

CORPORATE SOURCE: Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, La Jolla, CA, 92037, USA

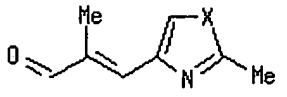
SOURCE: Chemistry--A European Journal (**1997**), 3(12), 1957-1970
CODEN: CEUJED; ISSN: 0947-6539

PUBLISHER: Wiley-VCH Verlag GmbH

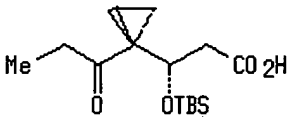
DOCUMENT TYPE: Journal

LANGUAGE: English

GI



I



III

AB For structure-activity relationship studies, two series of epothilone A analogs have been designed and synthesized, one contg. an oxazole moiety instead of the thiazole heterocycle and the other contg. a spirocyclopropane moiety in place of the gem-di-Me group at position C-4 (4,4-ethano-epothilones). The olefin metathesis strategy in soln. was utilized for the chem. synthesis of these compds. starting with key building blocks (I) (X = O), (S)-H2C=CH(CH2)3CH(Me)CHO (II), (S)-MeCH2COCMe2CH(OSiMe2CMe3)CH2CO2H for the oxazole series and building blocks I (X = S), II, and (III) for the 4,4-ethano series. The convergent strategy towards the designed epothilone A series involved: a- an aldol condensation reaction, b- an esterification reaction, c- an olefin metathesis reaction catalyzed by [RuCl2(=CHPh)-(PCy3)2], and d- epoxidn. of the macrocycle double bond.

IT **198475-12-6P**

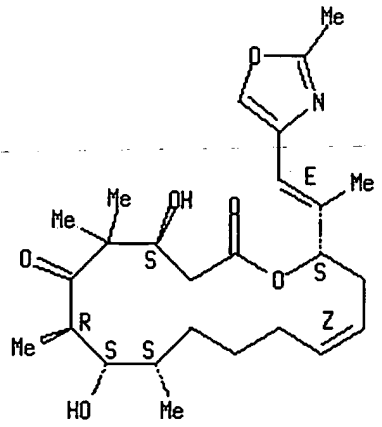
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(total synthesis of oxazole- and cyclopropane-contg. epothilone A analogs by the olefin metathesis approach)

RN 198475-12-6 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-oxazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L6 ANSWER 18 OF 35 HCAPLUS COPYRIGHT 2002 ACS

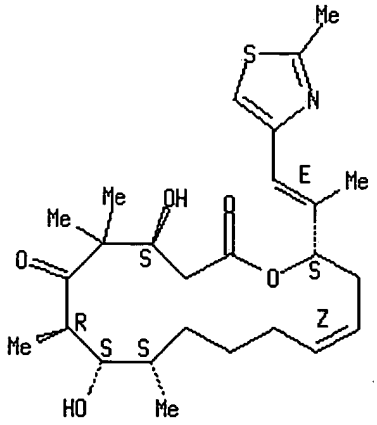
Full Text | Citing References

ACCESSION NUMBER: 1998:729 HCAPLUS
DOCUMENT NUMBER: 128:88685
TITLE: Metathesis vs metastasis: the chemistry and biology of the epothilones
AUTHOR(S): Finlay, Ray
CORPORATE SOURCE: Dep. Chemistry, The Skaggs Inst. for Chemical Biol., The Scripps Res. Inst., La Jolls, CA, 92037, USA
SOURCE: Chemistry & Industry (London) (**1997**), (24), 991-996
CODEN: CHINAG; ISSN: 0009-3068
PUBLISHER: Society of Chemical Industry
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 15 refs. on a recent entry onto the scene of potentially useful natural products, the epothilones A - E, providing valuable information for the fight against cancer via their interaction with microtubules.

IT **186692-73-9P**, Epothilone C
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation); USES (Uses)
(chem. and bioactivity of the epothilones)
RN 186692-73-9 HCAPLUS
CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.

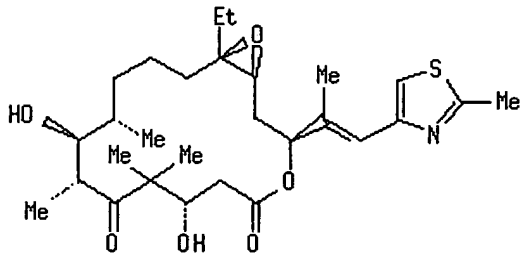


L6 ANSWER 19 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

ACCESSION NUMBER: 1997:787450 HCAPLUS
DOCUMENT NUMBER: 128:101936
TITLE: Total synthesis of 26-hydroxyepothilone B and related analogs
AUTHOR(S): Nicolaou, K. C.; Ninkovic, Sacha; Finlay, M. Ray V.; Sarabia, Francisco; Li, Tianhu
CORPORATE SOURCE: Department of Chemistry and Biochemistry, University of California, California, 92093, USA
SOURCE: Chemical Communications (Cambridge) (**1997**), (24), 2343-2344

CODEN: CHCOFS; ISSN: 1359-7345
PUBLISHER: Royal Society of Chemistry
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 128:101936
GI



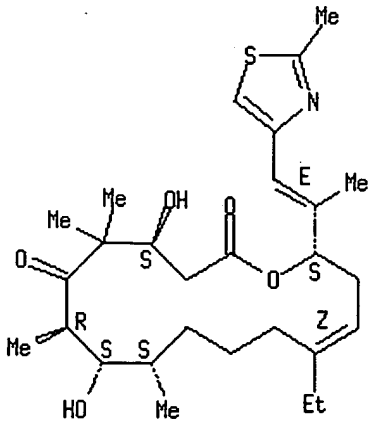
I

AB A series of 26-substituted epothilones B, e.g. I, were constructed by total synthesis involving a selective Wittig olefination, an aldol reaction and a macrolactonization as key steps.

IT **198475-04-6P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(total synthesis of 26-hydroxyepothilone B and related analogs)

RN 198475-04-6 HCAPLUS
CN Oxacyclohexadec-13-ene-2,6-dione, 13-ethyl-4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



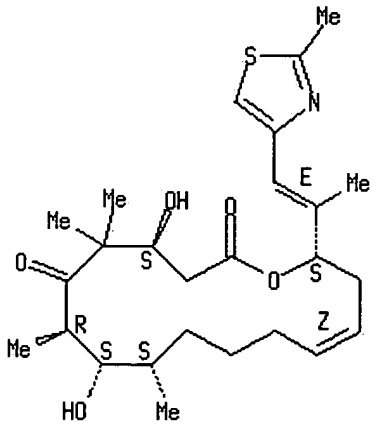
L6 ANSWER 20 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

ACCESSION NUMBER: 1997:724919 HCAPLUS
DOCUMENT NUMBER: 127:346221
TITLE: Synthesis of epothilones A and B in solid and solution phase. [Erratum to document cited in CA127:4950]
AUTHOR(S): Nicolaou, K. C.; Winssinger, N.; Pastor, J.; Ninkovic, S.; Sarabia, F.; He, Y.; Vourloumis, D.; Yang, Z.; Li, T.; Giannakakou, P.; Hamel, E.
CORPORATE SOURCE: Dep. Chemistry, Skaggs Inst. Chem. Biology, Scripps Res. Inst., La Jolla, CA, 92037, USA
SOURCE: Nature (London) (**1997**), 390(6655), 100

CODEN: NATUAS; ISSN: 0028-0836
PUBLISHER: Macmillan Magazines
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Ref. 19, includes, in addn. to a total synthesis of epothilone B, biol. data for compd. 23 and other congeners similar to the reported in the Letter.
IT **186692-73-9P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of a combinatorial library via solid-phase synthesis of epothilone A and soln.-phase synthesis of epothilone B (Erratum))
RN 186692-73-9 HCAPLUS
CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L6 ANSWER 21 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

ACCESSION NUMBER: 1997:714315 HCAPLUS
DOCUMENT NUMBER: 128:3560
TITLE: Designed epothilones: combinatorial synthesis, tubulin assembly properties, and cytotoxic action against taxol-resistant tumor cells
AUTHOR(S): Nicolaou, K. C.; Vourloumis, Dionisios; Li, Tianhu; Pastor, Joaquin; Winssinger, Nicolas; He, Yun; Ninkovic, Sacha; Sarabia, Francisco; Vallberg, Hans; Roschangar, Frank; King, N. Paul; Finlay, M. Ray V.; Giannakakou, Pareskevi; Verdier-Pinard, Pascal; Hamel, Ernest
CORPORATE SOURCE: Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, La Jolla, CA, 92037, USA
SOURCE: Angewandte Chemie, International Edition in English (**1997**), 36(19), 2097-2103
CODEN: ACIEAY; ISSN: 0570-0833
PUBLISHER: Wiley-VCH
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The title work demonstrates the power of interfacing combinatorial chem. with chem. biol. as facilitated by solid-phase synthesis, radiofrequency encoded combinatorial chem. and modern biol. assays. A library of 112 epothilones were prepd. by solid-phase synthesis, their structure activity

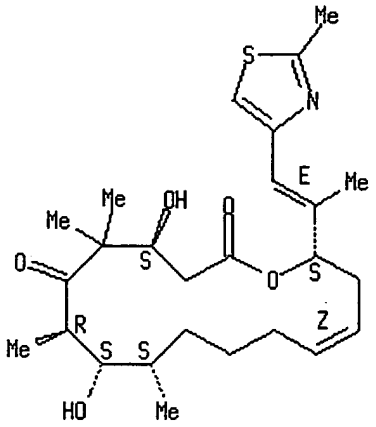
relationships measured by tubulin binding assay and some tested for inhibition of carcinoma cell growth.

IT **186692-73-9P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(combinatorial synthesis of epothilone library, tubulin assembly properties, and cytotoxic action against taxol-resistant tumor cells)

RN 186692-73-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L6 ANSWER 22 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

ACCESSION NUMBER: 1997:714314 HCAPLUS
DOCUMENT NUMBER: 127:358730
TITLE: Structure-activity relationships of the epothilones and the first in vivo comparison with paclitaxel
AUTHOR(S): Su, Dai-Shi; Balog, Aaron; Meng, Dongfang; Bertinato, Peter; Danishefsky, Samuel J.; Zheng, Yu-Huang; Chou, Ting-Chao; He, Lifeng; Horwitz, Susan B.
CORPORATE SOURCE: Laboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, New York, NY, 10021, USA
SOURCE: Angewandte Chemie, International Edition in English (**1997**), 36(19), 2093-2096
CODEN: ACIEAY; ISSN: 0570-0833
PUBLISHER: Wiley-VCH
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The structure-activity relationships of the epothilones and 18 derivs. and analogs were studied. An in vivo comparison of the chemotherapeutic effect of epothilone B with that of paclitaxel was also studied. The chemotherapeutic effect of daily doses of epothilone B (0.7 mg/kg) and paclitaxel (2 mg/kg) in CB-17 SCID mice bearing drug-resistant human CCRF-CEM/VBL xenografts were T/C = 0.33 and T/C = 0.70, resp.

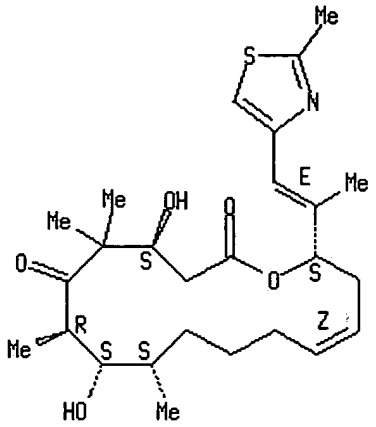
IT **186692-73-9**, Desoxyepothilone A
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(structure-activity relationships of the epothilones and in vivo comparison with paclitaxel)

RN 186692-73-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-

[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.

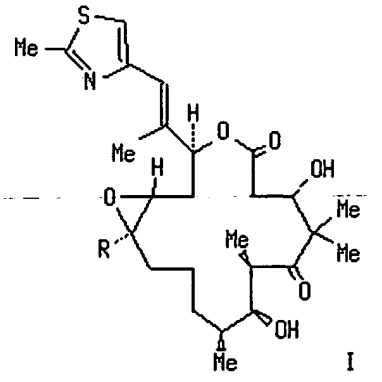


L6 ANSWER 23 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

ACCESSION NUMBER:	1997:665094 HCAPLUS
DOCUMENT NUMBER:	127:293040
TITLE:	Total Syntheses of Epothilones A and B
AUTHOR(S):	Meng, Dongfang; Bertinato, Peter; Balog, Aaron; Su, Dai-Shi; Kamenecka, Ted; Sorensen, Erik; Danishefsky, Samuel J.
CORPORATE SOURCE:	Laboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, New York, NY, 10021, USA
SOURCE:	Journal of the American Chemical Society (**1997**), 119(42), 10073-10092 CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER:	American Chemical Society
DOCUMENT TYPE:	Journal
LANGUAGE:	English
OTHER SOURCE(S):	CASREACT 127:293040

GI



I

AB Convergent, stereocontrolled total syntheses of the microtubule-stabilizing macrolides epothilones A (I; R = H) and B (I; R = Me) have

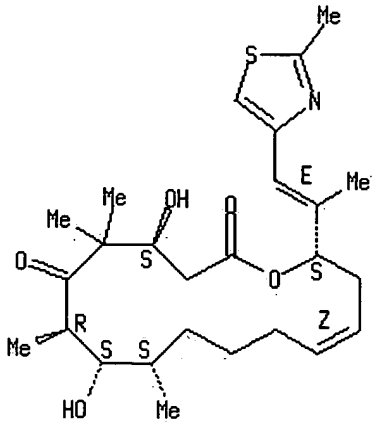
been achieved. Four distinct ring-forming strategies were pursued. Of these four, three were reduced to practice. In one approach, the action of a base on a substance possessing an acetate ester and a nonenolizable aldehyde brought about a remarkably effective macroaldolization simultaneously creating the C2-C3 bond and the hydroxyl-bearing stereocenter at C-3. Alternatively, the 16-membered macrolide of the epothilones could be fashioned through a C12-C13 ring-closing olefin metathesis and through macrolactonization of the appropriate hydroxy acid. The application of a stereospecific B-alkyl Suzuki coupling strategy permitted the establishment of a cis C12-C13 olefin, thus setting the stage for an eventual site- and diastereoselective epoxidn. reaction. The development of a novel cyclopropane solvolysis strategy for incorporating the geminal Me groups of the epothilones, and the use of Lewis acid catalyzed diene-aldehyde cyclocondensation (LACDAC) and asym. allylation methodol. are also noteworthy.

IT **186692-73-9P**, (-)-Desoxyepothilone A
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(syntheses of epothilones A and B via macroaldolization, olefin metathesis and macrolactonization)

RN 186692-73-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L6 ANSWER 24 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

ACCESSION NUMBER: 1997:528753 HCAPLUS
DOCUMENT NUMBER: 127:135660
TITLE: Total Syntheses of Epothilones A and B via a Macrolactonization-Based Strategy
AUTHOR(S): Nicolaou, K. C.; Ninkovic, S.; Sarabia, F.; Vourloumis, D.; He, Y.; Vallberg, H.; Finlay, M. R. V.; Yang, Z.
CORPORATE SOURCE: Department of Chemistry and The Skaggs, Institute for Chemical Biology, La Jolla, CA, 92037, USA
SOURCE: Journal of the American Chemical Society (1997), 119(34), 7974-7991
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 127:135660
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

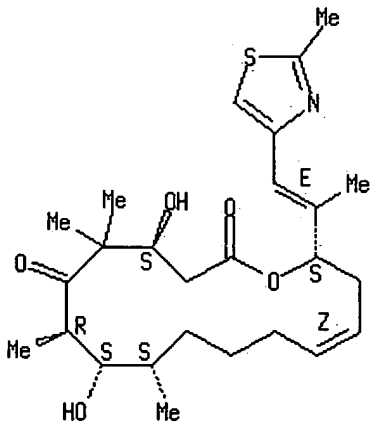
AB The total syntheses of epothilones A (I) (R = H) and B I (R = Me) and several analogs are described. The reported strategy relies on a macrolactonization approach and features selective epoxidn. of the macrocycle double bond in precursors II (R = H, Me) as well as high convergency and flexibility. Building blocks (S)-MeCH2COC(Me)2CH(OSiMe2CMe3)CH2CO2H, (S)-Me3CMe2SiOCH2CH(Me)CH2CH2CH2COR (R = H, Me), (III) [R2 = CH2CH2P+(Ph)3I-; CH2CHO] were constructed by asym. processes and coupled via Wittig, aldol, and macrolactonization reactions to afford the basic skeleton of epothilones and that of several of their analogs by a relatively short route. The utilization of intermediate III [R2 = (E)-CH2CH=C(Me)CH2CH2CH2I], obtained via a stereoselective Wittig reaction and its Enders coupling to SAMP hydrazone, in combination with a stereoselective aldol reaction with the modified substrate (S)-MeCH2COC(Me)2CH(OSiMe2CMe3)CH2CH2OSiMe2CMe3 improved the stereoselectivity and efficiency of the total synthesis of these new and highly potent microtubule binding antitumor agents.

IT **186692-73-9P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(total syntheses of epothilones A and B via a macrolactonization-based strategy)

RN 186692-73-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L6 ANSWER 25 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

ACCESSION NUMBER: 1997:528752 HCAPLUS
DOCUMENT NUMBER: 127:149021
TITLE: The Olefin Metathesis Approach to Epothilone A and Its Analogs
AUTHOR(S): Nicolaou, K. C.; He, Y.; Vourloumis, D.; Vallberg, H.; Roschangar, F.; Sarabia, F.; S.Ninkovic; Yang, Z.; Trujillo, J. I.
CORPORATE SOURCE: Department of Chemistry and The Skaggs, Institute for Chemical Biology, La Jolla, CA, 92037, USA
SOURCE: Journal of the American Chemical Society (**1997**),

119(34), 7960-7973
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 127:149021

GI For diagram(s), see printed CA Issue.

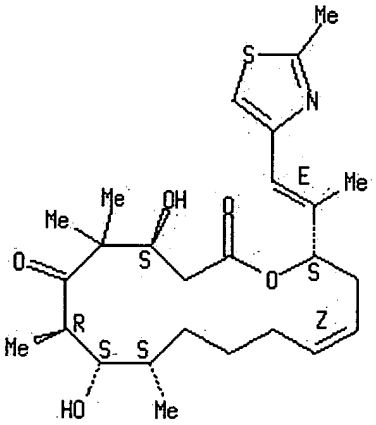
AB The olefin metathesis approach to epothilone A (I) and several diastereomeric analogs is described. Key building blocks II, (S)-OHCCH(Me)CH2CH2CH2CH=CH2, and (S)-MeCH2COC(Me)2CH(OSiMe2CMe3)CH2CO2H were constructed in optically active form and were coupled and elaborated to olefin metathesis precursor III (R = SiMe2CMe3) via an aldol reaction and an esterification coupling. Olefin metathesis of compd. III (R = SiMe2CMe3), under the catalytic influence of RuCl2(:CHPh)(PCy3)2, furnished cis- and trans-cyclic olefins IV (R = SiMe2CMe3). Epoxidn. of (Z)-IV (R = H) gave I and several analogs, whereas epoxidn. of (E)-IV (R = H) resulted in addnl. epothilones. Similar elaboration of isomeric as well as simpler intermediates resulted in yet another series of epothilone analogs and model systems.

IT **186692-73-9P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis of epothilone A and analogs via olefin metathesis)

RN 186692-73-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L6 ANSWER 26 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

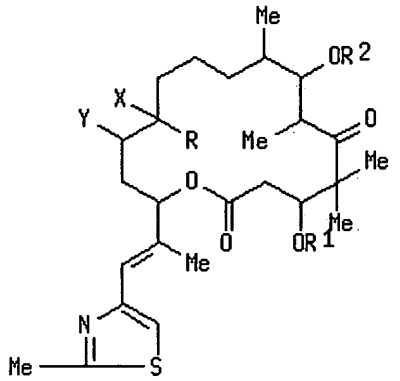
ACCESSION NUMBER: 1997:456769 HCAPLUS
DOCUMENT NUMBER: 127:50474
TITLE: Preparation of epothilone derivatives as agrochemicals and pharmaceuticals
INVENTOR(S): Hoefle, Gerhard; Kiffe, Michael
PATENT ASSIGNEE(S): Gesellschaft fuer Biotechnologische Forschung Mbh (Gbf), Germany
SOURCE: Ger. Offen., 9 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19542986	**A1**	**19970522**	**DE 1995-19542986**	**19951117**
WO 9719086	**A1**	**19970529**	**WO 1996-EP5080**	**19961118**
W: JP, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 873341	A1	19981028	EP 1996-939097	19961118
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
EP 903348	A1	19990324	EP 1998-121523	19961118
EP 903348	B1	20020605		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2000500757	T2	20000125	JP 1997-519381	19961118
EP 1186606	A1	20020313	EP 2001-127352	19961118
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
AT 218556	E	20020615	AT 1998-121523	19961118
US 6288237	B1	20010911	US 1998-77055	19980803
US 2001034452	A1	20011025	US 2001-836134	20010416

PRIORITY APPLN. INFO.:
DE 1995-19542986 A 19951117
DE 1996-19639456 A 19960925
EP 1996-939097 A3 19961118
WO 1996-EP5080 W 19961118
US 1998-77055 A3 19980803

OTHER SOURCE(S): MARPAT 127:50474

GI



I

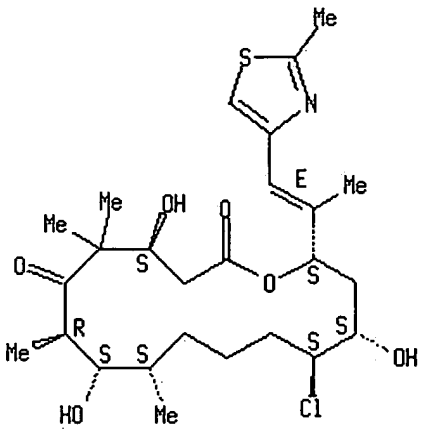
AB The title compds., e.g., I [R = H, C1-4 alkyl; R1, R2 = H, C1-6 alkyl, C1-6 acyl, benzoyl, C1-4 trialkylsilyl, benzyl, Ph, C1-6 alkoxy, C6 alkyl-, hydroxy-, and halo-substituted benzyl or phenyl; X, Y = halo, OH, acyloxy, alkoxy, benzoyloxy] , useful as agrochems. and pharmaceuticals (no data), are prepd. Thus, epothilone A in acetone contg. trifluoroacetic acid was heated overnight at 50° and the reaction mixt. was adjusted to pH 7 with 1 M phosphate buffer to give 2 isomers, each in 19% yield.

IT **191105-82-5P**
RL: AGR (Agricultural use); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of epothilone derivs. as agrochems. and pharmaceuticals)

RN 191105-82-5 HCAPLUS

CN Oxacyclohexadecane-2,6-dione, 13-chloro-4,8,14-trihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, [4R*,7S*,8R*,9R*,13R*,14R*,16R*(E)]- (9CI) (CA INDEX NAME)

Relative stereochemistry.
Double bond geometry as shown.



L6 ANSWER 27 OF 35 HCAPLUS COPYRIGHT 2002 ACS

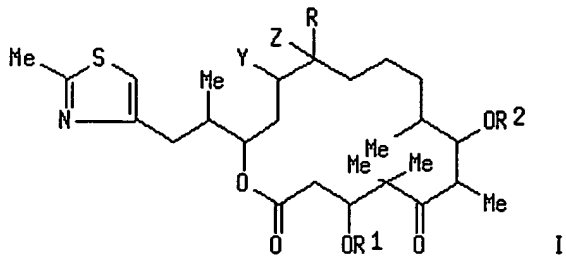
Full Text | Citing References

ACCESSION NUMBER: 1997:443365 HCAPLUS
DOCUMENT NUMBER: 127:81289
TITLE: Preparation of epothilone derivatives as agrochemicals and pharmaceuticals
INVENTOR(S): Hofle, Gerhard; Kiffe, Michael
PATENT ASSIGNEE(S): Gesellschaft Fur Biotechnologische Forschung Mbh (Gbf), Germany; Hofle, Gerhard; Kiffe, Michael
SOURCE: PCT Int. Appl., 38 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9719086	**A1**	**19970529**	**WO 1996-EP5080**	**19961118**
W: JP, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
DE 19542986	**A1**	**19970522**	**DE 1995-19542986**	**19951117**
DE 19639456	**A1**	**19980326**	**DE 1996-19639456**	**19960925**
EP 873341	A1	19981028	EP 1996-939097	19961118
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2000500757	T2	20000125	JP 1997-519381	19961118
US 6288237	B1	20010911	US 1998-77055	19980803

PRIORITY APPLN. INFO.:
DE 1995-19542986 A 19951117
DE 1996-19639456 A 19960925
WO 1996-EP5080 W 19961118

OTHER SOURCE(S): MARPAT 127:81289
GI



I

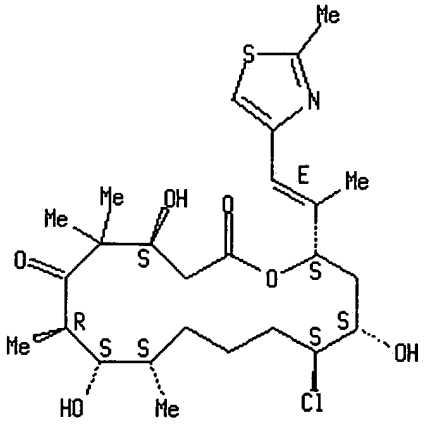
AB The title compds., e.g., I [R = H, C1-4 alkyl; R1, R2 = H, C1-6 alkyl, C1-6 acyl, benzoyl, C1-4 trialkylsilyl, benzyl, Ph, C1-6 alkoxy, C6 alkyl-, hydroxy-, and halo-substituted benzyl or phenyl; X, Y = H, halo, pseudohalo, OH, acyloxy, alkoxy, benzoyloxy; or YZ = O, bond; however, I may not be epothilone A or B] , useful as agrochems. and pharmaceuticals (no data), are prepd. Thus, epothilone A in acetone contg. trifluoroacetic acid was heated overnight at 50° and the reaction mixt. was adjusted to pH 7 with 1 M phosphate buffer to give 2 isomers, each in 19% yield.

IT **191105-82-5P**
RL: AGR (Agricultural use); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of epothilone derivs. as agrochems. and pharmaceuticals)

RN 191105-82-5 HCAPLUS

CN Oxacyclohexadecane-2,6-dione, 13-chloro-4,8,14-trihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, [4R*,7S*,8R*,9R*,13R*,14R*,16R*(E)]- (9CI) (CA INDEX NAME)

Relative stereochemistry.
Double bond geometry as shown.



L6 ANSWER 28 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

ACCESSION NUMBER: 1997:430309 HCAPLUS
DOCUMENT NUMBER: 127:108793
TITLE: Stereoselective syntheses and evaluation of compounds in the 8-desmethylepothilone A series: some surprising observations regarding their chemical and biological properties
AUTHOR(S): Balog, Aaron; Betinato, Peter; Su, Dai-Shi; Meng, Dongfang; Sorensen, Erik; Danishefsky, Samuel J.; Zheng, Yu-Huang; Chou, Ting-Chao; He, Lifeng; Horwitz, Susan B.
CORPORATE SOURCE: Lab. Bioorganic Chem., Sloan-Kettering Inst. Cancer Res., New York, NY, 10021, USA

SOURCE: Tetrahedron Letters (**1997**), 38(26), 4529-4532
CODEN: TELEAY; ISSN: 0040-4039
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 127:108793

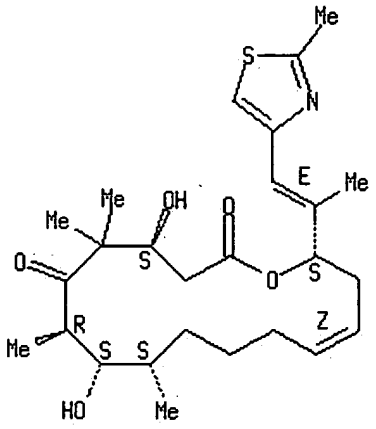
AB The title compds. have been synthesized in a convergent way by recourse to a Weiler type dianion construction.

IT **186692-73-9**, Desoxyepothilone A
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(stereoselective syntheses and evaluation of compds. in the 8-desmethylepothilone A series)

RN 186692-73-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

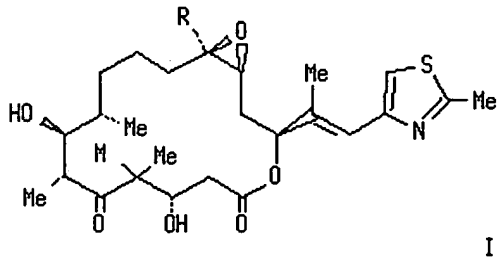
Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L6 ANSWER 29 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

ACCESSION NUMBER: 1997:330310 HCAPLUS
DOCUMENT NUMBER: 127:4950
TITLE: Synthesis of epothilones A and B in solid and solution phase
AUTHOR(S): Nicolaou, K. C.; Winssinger, N.; Pastor, J.; Ninkovic, S.; Sarabia, F.; He, Y.; Vourloumis, D.; Yang, Z.; Li, T.; Giannakakou, P.; Hamel, E.
CORPORATE SOURCE: Dep. Chemistry, Skaggs Inst. Chem. Biology, Scripps Res. Inst., La Jolla, CA, 92037, USA
SOURCE: Nature (London) (**1997**), 387(6630), 268-272
CODEN: NATUAS; ISSN: 0028-0836
PUBLISHER: Macmillan Magazines
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 127:4950
GI



I

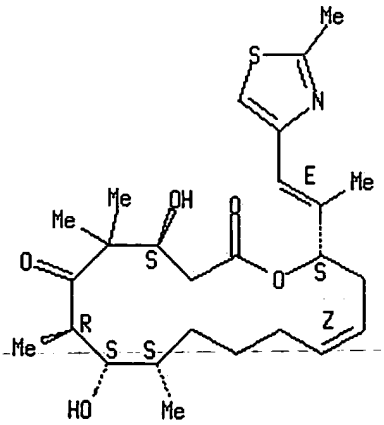
AB Epothilones A (I; R = H) and B (I: R = Me), two compds. that were recently isolated from myxobacterium Sorangium cellulosum strain 90, have generated intense interest among chemists, biologists and clinicians owing to the structural complexity, unusual mechanism of interaction with microtubules and anticancer potential of these mols. Like taxol, they exhibit cytotoxicity against tumor cells by inducing microtubule assembly and stabilization, even in taxol-resistant cell lines. Following the structural elucidation of these mols. by X-ray crystallog. in 1996, several synthesis of epothilones A and B have been reported, indicative of the potential importance of these mols. in the cancer field. Here we report the first solid-phase synthesis of epothilone A, the total synthesis of epothilone B, and the generation of a small epothilone library. The solid-phase synthesis applied here to epothilone A could open up new possibilities in natural-product synthesis and, together with soln.-phase synthesis of other epothilones, paves the way for the generation of large combinatorial libraries of these important mols. for biol. screening.

IT **186692-73-9P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of a combinatorial library via solid-phase synthesis of epothilone A and soln.-phase synthesis of epothilone B)

RN 186692-73-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L6 ANSWER 30 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

ACCESSION NUMBER: 1997:302059 HCAPLUS
DOCUMENT NUMBER: 127:4948
TITLE: Total synthesis of (-)-epothilone B: an extension of

	the Suzuki coupling method and insights into structure-activity relationships of the epothilones
AUTHOR(S):	Su, Dai-Shi; Meng, Dongfang; Bertinato, Peter; Balog, Aaron; Sorensen, Erik J.; Danishefsky, Samuel J.; Zheng, Yu-Huang; Chou, Ting-Chao; He, Lifeng; Horwitz, Susan B.
CORPORATE SOURCE:	Laboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, New York, NY, 10021, USA
SOURCE:	Angewandte Chemie, International Edition in English (**1997**), 36(7), 757-759 CODEN: ACIEAY; ISSN: 0570-0833
PUBLISHER:	VCH
DOCUMENT TYPE:	Journal
LANGUAGE:	English
OTHER SOURCE(S):	CASREACT 127:4948
GI	

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

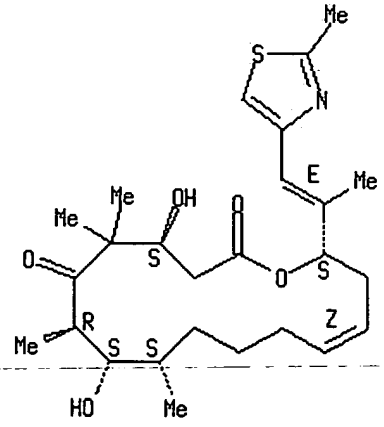
AB (-)-Epothilone B (I; R = Me, X = O) and desoxyepothilone B (I; R = Me, X = bond) were prepd. via Suzuki coupling of (Z)-vinyl iodide II with borane III. I (R = H, Me, X = O, bond) and the E-isomers of I (R = H, Me, X = bond) were tested for efficacy against drug-sensitive and resistant CCRF-CEM cell lines (IC50 = 0.0004 - 0.262 μM).

IT **186692-73-9**, Desoxyepothilone A
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(synthesis of epothilone B via a Suzuki coupling and insights into antitumor structure-activity relationships)

RN 186692-73-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L6 ANSWER 31 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

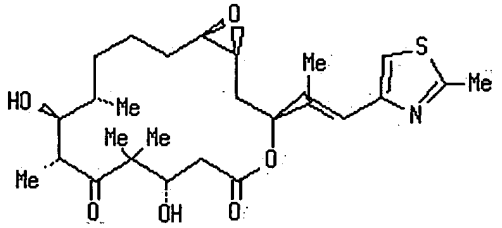
ACCESSION NUMBER:	1997:206419 HCAPLUS
DOCUMENT NUMBER:	126:251010
TITLE:	Total synthesis of epothilone A: the

macrolactonization approach

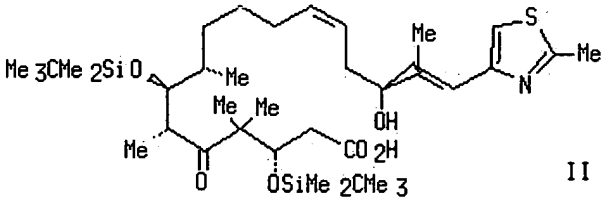
AUTHOR(S): Nicolaou, K. C.; Sarabia, Francisco; Ninkovic, Sacha; Yang, Zhen
CORPORATE SOURCE: Dep. Chem., Skaggs Inst. Chem. Biol. Scripps Res. Inst., La Jolla, CA, 92037, USA

SOURCE: Angewandte Chemie, International Edition in English (**1997**), 36(5), 525-527
CODEN: ACIEAY; ISSN: 0570-0833
PUBLISHER: VCH
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 126:251010

GI



I



II

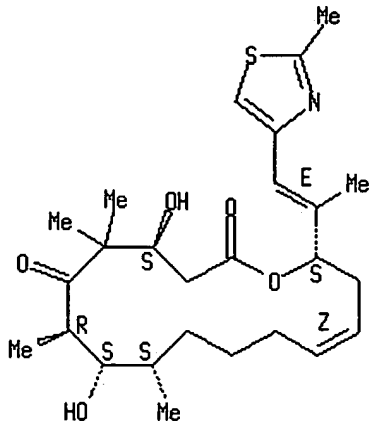
AB Epothilone A (I) was prepd. via a highly convergent and flexible route with macrolactonization of hydroxy acid II as the key step.

IT **186692-73-9P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(total synthesis of epothilone A via a macrolactonization approach)

RN 186692-73-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

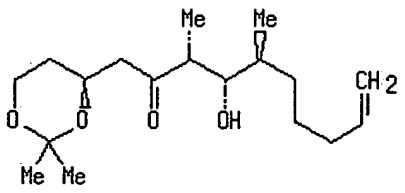
Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



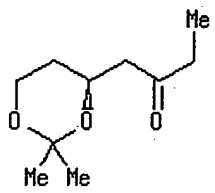
L6 ANSWER 32 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

ACCESSION NUMBER: 1997:206418 HCAPLUS
DOCUMENT NUMBER: 126:277316
TITLE: Total synthesis of (-)-epothilone A
AUTHOR(S): Schinzer, Dieter; Limberg, Anja; Bauer, Armin; Boehm, Oliver M.; Cordes, Martin
CORPORATE SOURCE: Dip. Chim., Inst. Org. Chem. Tech. Univ. Hagenring, Braunschweig, D-38106, Germany
SOURCE: Angewandte Chemie, International Edition in English (**1997**), 36(5), 523-524
CODEN: ACIEAY; ISSN: 0570-0833
PUBLISHER: VCH
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 126:277316
GI



I



II

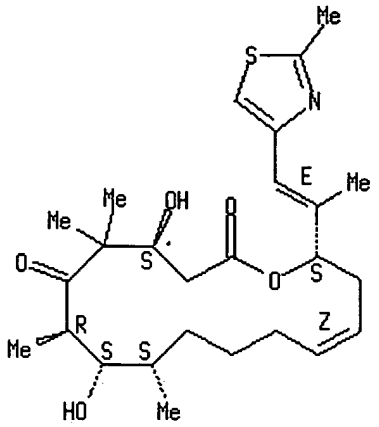
AB Stereoselective total synthesis of (-)-epothilone A and epothilone C was reported. The key step was the diastereoselective prepn. of intermediate ketone I by an aldol condensation of II with (S)-2-methyl-6-heptenal.

IT **186692-73-9P**, Epothilone C
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(total synthesis of (-)-epothilone A)

RN 186692-73-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



L6 ANSWER 33 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

ACCESSION NUMBER:	1997:175662 HCAPLUS
DOCUMENT NUMBER:	126:225133
TITLE:	Remote Effects in Macrolide Formation through Ring-Forming Olefin Metathesis: An Application to the Synthesis of Fully Active Epothilone Congeners
AUTHOR(S):	Meng, Dongfang; Su, Dai-Shi; Balog, Aaron; Bertinato, Peter; Sorensen, Erik J.; Danishefsky, Samuel J.; Zheng, Yu-Huang; Chou, Ting-Chao; He, Lifeng; Horwitz, Susan B.
CORPORATE SOURCE:	Laboratories for Bioorganic Chemistry and Biochemical Pharmacology, Sloan-Kettering Institute for Cancer Research, New York, NY, 10021, USA
SOURCE:	Journal of the American Chemical Society (**1997**), 119(11), 2733-2734 CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER:	American Chemical Society
DOCUMENT TYPE:	Journal
LANGUAGE:	English
OTHER SOURCE(S):	CASREACT 126:225133

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

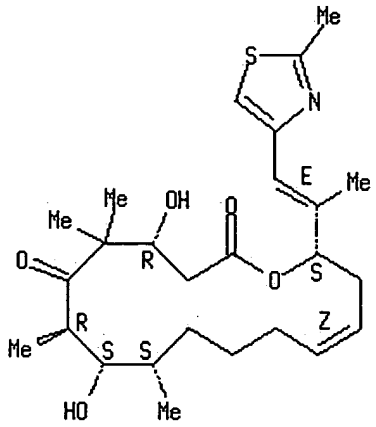
AB A ring closing olefin metathesis strategy for the synthesis of the previously encountered desoxyepothilone A (I) is described. A merging of the alkyl segment II (carbons 12-21) and acyl segment III (carbons 3-11) through an intermol. aldol-condensation reaction provided substrates needed for ring closing olefin metathesis. Thus, thiazole IV underwent olefin metathesis in C6H6 contg. 50 mol % (PhCH:)[P(cyclohexyl)3]2RuCl2 to give 65% II and its E-isomer (Z:E 1:2). The results of these cyclization indicate a remarkable sensitivity to permutations of functionality at centers remote from the site of olefin metathesis. The in vitro biol. activity of E and Z desoxyepothilone as well as several related congeners is also described. I has IC50 range of 0.012-0.022 μM against drug-sensitive and -resistant human leukemic CCRF-CEM cell lines.

IT **188259-95-2P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of antitumor epothilone congeners via ring-forming olefin metathesis)

RN 188259-95-2 HCAPLUS
CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4R,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

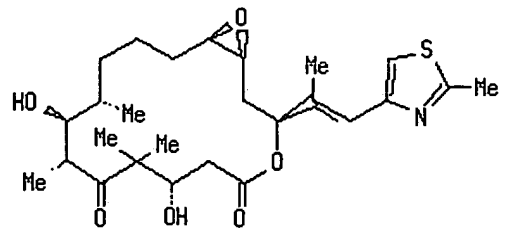
Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



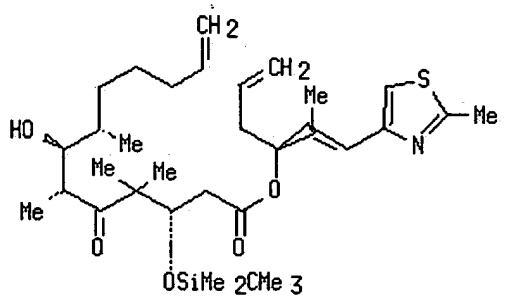
L6 ANSWER 34 OF 35 HCAPLUS COPYRIGHT 2002 ACS

Full Text | Citing References

ACCESSION NUMBER: 1997:117381 HCAPLUS
DOCUMENT NUMBER: 126:199371
TITLE: Total synthesis of epothilone A: the olefin metathesis approach
AUTHOR(S): Yang, Zhen; He, Yun; Vourloumis, Dionisios; Vallberg, Hans; Nicolaou, K. C.
CORPORATE SOURCE: Department Chemistry Skaggs Institute Chemical Biology, Scripps Research Institute, La Jolla, CA, 92037, USA
SOURCE: Angewandte Chemie, International Edition in English (**1997**), 36(1/2), 166-168
CODEN: ACIEAY; ISSN: 0570-0833
PUBLISHER: VCH
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 126:199371
GI



I



II

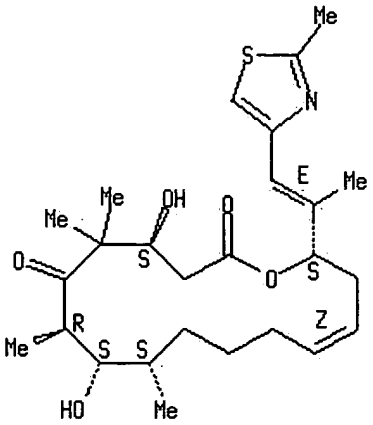
AB The asym. total synthesis of epothilone A (I) from EtCOCMe2CHO, (S)-H2C:CH(CH2)3CHMeCHO and Et 2-methylthiazole-4-carboxylate via metathesis of olefin II is described.

IT **186692-73-9P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(total synthesis of epothilone A via an olefin metathesis)

RN 186692-73-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.

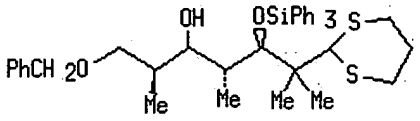


L6 ANSWER 35 OF 35 HCAPLUS COPYRIGHT 2002 ACS

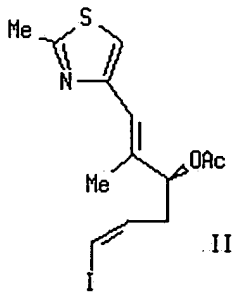
Full Text | Citing References

ACCESSION NUMBER: 1997:72321 HCAPLUS
DOCUMENT NUMBER: 126:144023
TITLE: Total synthesis of (-)-epothilone A
AUTHOR(S): Balog, Aaron; Meng, Dongfang; Kamenecka, Ted; Bertinato, Peter; Su, Dai-Shi; Sorensen, Erik J.; Danishefsky, Samuel J.
CORPORATE SOURCE: Lab. for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, New York, NY, 10021,

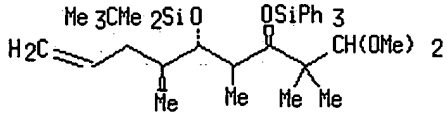
USA
SOURCE: Angewandte Chemie, International Edition in English (1997), Volume Date 1996, 35(23/24), 2801-2803
CODEN: ACIEAY; ISSN: 0570-0833
PUBLISHER: VCH
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I



II



III

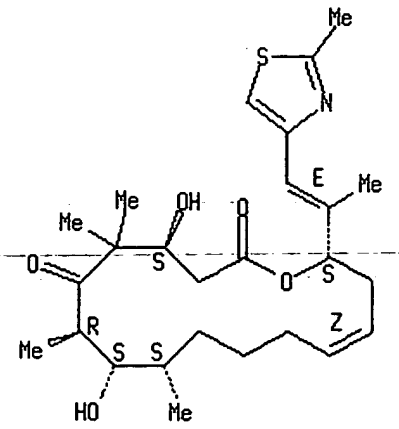
AB (-)-Epothilone A was prepd. from dithiane I, (R)-glycidol and [(2-methyl-1,3-thiazol-4-yl)methyl]diphenylphosphine oxide via a B-alkyl Suzuki coupling of thiazole II with acetal III followed by closure of the macrocycle with an aldol reaction.

IT **186692-73-9P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(total synthesis of (-)-epothilone A via a B-alkyl Suzuki coupling followed by closure of the macrocycle with an aldol reaction)

RN 186692-73-9 HCAPLUS

CN Oxacyclohexadec-13-ene-2,6-dione, 4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (4S,7R,8S,9S,13Z,16S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



=> **file caold**
COST IN U.S. DOLLARS SINCE FILE TOTAL

```
                                                        ENTRY    SESSION
FULL ESTIMATED COST                                    162.28     305.05

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)        SINCE FILE      TOTAL
                                                        ENTRY    SESSION
CA SUBSCRIBER PRICE                                    -22.30     -22.30

FILE 'CAOLD' ENTERED AT 18:18:24 ON 22 AUG 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2002 AMERICAN CHEMICAL SOCIETY (ACS)

FILE COVERS 1907-1966
FILE LAST UPDATED:  01 May 1997 (19970501/UP)

  This file contains CAS Registry Numbers for easy and accurate
  substance identification.  Title keywords, authors, patent
  assignees, and patent information, e.g., patent numbers, are
  now searchable from 1907-1966.  TIFF images of CA abstracts
  printed between 1907-1966 are available in the PAGE
  display formats.

  This file supports REGlstRY for direct browsing and searching of
  all substance data from the REGISTRY file.  Enter HELP FIRST for
  more information.

=> d his

     (FILE 'HOME' ENTERED AT 18:12:21 ON 22 AUG 2002)

     FILE 'REGISTRY' ENTERED AT 18:12:27 ON 22 AUG 2002
L1              STRUCTURE UPLOADED

     FILE 'REGISTRY' ENTERED AT 18:16:22 ON 22 AUG 2002
L2              STRUCTURE UPLOADED
L3           18 S L2
L4          292 S L2 FULL

     FILE 'HCAPLUS' ENTERED AT 18:17:16 ON 22 AUG 2002
L5          143 S L4
L6           35 S L5 AND PD < SEPTEMBER 1998

     FILE 'CAOLD' ENTERED AT 18:18:24 ON 22 AUG 2002

=> s l4
L7            0 L4

=> log y
COST IN U.S. DOLLARS                              SINCE FILE      TOTAL
                                                        ENTRY    SESSION
FULL ESTIMATED COST                                     0.38     305.43

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)        SINCE FILE      TOTAL
                                                        ENTRY    SESSION
CA SUBSCRIBER PRICE                                     0.00     -22.30

STN INTERNATIONAL LOGOFF AT 18:18:36 ON 22 AUG 2002
```